N-Methyl-D-aspartate (NMDA) receptor-based treatment approaches in schizophrenia: the first decade

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Abstract
The study of excitatory amino acids (EAA) [e.g. glutamate (Glu), aspartate] as neurotransmitters has resulted in many new and fundamental concepts in neuroscience. Much of this progress centres upon the role of N-methyl-D-aspartate (NMDA) subtype of Glu receptors in central nervous system synaptic transmission and plasticity. A leading hypothesis suggests that deficits in NMDA receptor-mediated neurotransmission may be central to the pathophysiology of schizophrenia. The conceptual foundation of this hypothesis derives from the clinical effects of NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine and from post-mortem findings in brain samples of schizophrenia patients. Consequently, at present there is an intense search for pharmacological strategies capable of facilitating NMDA receptor function in this illness. During the last decade, a first generation of small clinical studies has focused on assessing the therapeutic potential of glycine (Gly) site agonists of the NMDA receptor, such as Gly, d-serine and d-cycloserine. The results of these studies indicate that this type of compound may reduce negative symptoms and executive cognitive deficits in schizophrenia patients. Furthermore, preliminary findings suggest that patients having low serum Gly levels may represent the population of choice for treatment with Gly-site agonists. Additional potential schizophrenia treatments that may affect mainly NMDA receptor neurotransmission are: (i) other full and partial Gly-site agonists – in course of development for clinical use, and (ii) Gly transport antagonists that can inhibit Gly reuptake from neuronal synapses. Moreover, the antipsychotic action of some typical and atypical neuroleptics may be mediated by their agonistic activity at the strychnine-insensitive NMDA receptor-associated Gly site. After decades of relative neglect, the role of glutamatergic neurotransmission in the pathophysiology and therapeutics of schizophrenia is presently in process of conceptualization. In this context, it is likely that the development of NMDA receptor-based approaches for the treatment of this illness will continue. This trend is already supported by available clinical findings with Gly-site agonists and may herald an important, innovative development in the pharmacological treatment of neuropsychiatric syndromes.

Received 11 January 2000; Reviewed 29 March 2000; Revised 7 May 2000; Accepted 14 May 2000

Key words: Schizophrenia, NMDA receptor, glycine-site agonists, glycine, d-serine, d-alanine, d-cycloserine, typical and atypical antipsychotics, glycine reuptake inhibitors.

Introduction
Based upon the well-characterized pharmacological actions and clinical effects of dopamine receptor antagonists, schizophrenia has been traditionally associated, for nearly half-century, with disturbances in dopaminergic functioning. Accumulating basic science (for review, see Tamminga, 1998) and clinical data suggest a complementary illness model that implicates brain glutamatergic abnormalities in the pathophysiology of schizophrenia. Until recently, the human psychopharmacology of glutamatergic systems has been neglected relative to monoaminergic and cholinergic systems, although most of excitatory neuronal transmission in the central nervous system (CNS) is mediated by the endogenous excitatory amino acid (EAA), glutamate (Glu) and its congeners – aspartate and homocysteine (Greenamyre and Porter, 1994). Because excitatory transmission also stimulates neuronal inhibition, the firing of almost every CNS neuron is heavily modulated by glutamatergic neurotransmission. Furthermore, reciprocal control mechanisms covering glutamatergic and dopaminergic systems may be operational in providing an optimal feedback from basal ganglia and thalamus to cortex (Carlsson and...
A leading glutamatergic hypothesis of schizophrenia suggests that deficits in the function of N-methyl-D-aspartate (NMDA) subtype of Glu receptors may be central to the neurobiology of this illness (for review, see Javitt and Zukin, 1991a). This hypothesis is based on post-mortem studies of Glu receptor function in brain samples of schizophrenia patients (Ishimaru et al., 1994; Nishikawa et al., 1983; Toru et al., 1998; Tsai et al., 1995) and on the behavioural effects induced by NMDA receptor antagonists. The most compelling evidence linking NMDA receptor function with schizophrenia is provided by the psychotomimetic effects induced by phencyclidine (PCP) and ketamine. In patients with schizophrenia, these dissociative anaesthetics exacerbate existing psychotic symptoms and may re-activate symptoms in remission, without having new psychotomimetic effects (Lahti et al., 1995; Luby et al., 1959; Malhotra et al., 1997a), an action in which they are unique among other stimulants and psychotomimetics (Tamminga, 1998). The administration of PCP and ketamine to healthy volunteers reproduces many of the symptoms of schizophrenia, including positive symptoms, aspects of formal thought disorder, withdrawal behaviours and cognitive dysfunction (Krystal et al., 1994; Luby et al., 1959; Malhotra et al., 1996). In contrast, dopaminergic agents such as amphetamine or methylphenidate are known to induce primarily positive symptoms. PCP and ketamine induce their unique behavioural effects by binding to a site (i.e. PCP receptor) located within the ion channel associated with the NMDA receptor (Javitt and Zukin, 1991b). Binding of these compounds to this site leads to non-competitive blockade of NMDA receptor-mediated neurotransmission. Although their behavioural effects are less well characterized, competitive NMDA antagonists, which were developed as potential treatments for ischaemic brain damage and epilepsy, also appear to induce PCP-like behavioural effects in humans (Muir and Lees, 1995). The ability of both non-competitive and competitive NMDA receptor antagonists to induce schizophrenia-like psychotic symptoms indicates that endogenous dysfunction or dysregulation of NMDA receptor function may be critically implicated in the pathophysiology of schizophrenia. During the last decade, these new concepts have led to the first clinical trials attempting to assess the therapeutic potential of treatment approaches that aim at modulating NMDA receptor-mediated neurotransmission in schizophrenia.

The NMDA receptor as a target for drug development

The action of Glu and its congeners are mediated at three subtypes of ionotropic receptors – amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate and NMDA – and at two distinct families of metabotropic, G-protein-coupled receptors (for review, see Collingridge and Lester, 1989). Ionotropic receptors open cation-permeable channels to mediate either potassium or calcium flow and consist of specific protein subunits that have been cloned using molecular techniques (Hollman and Heinemann, 1994). These different receptor subunits can combine in homomeric or heteromeric fashion, forming a variety of multimeric combinations in different brain regions. Because the subunit composition of each receptor plays a critical role in determining its pharmacological properties, it is assumed that ionotropic receptors from different areas in the adult brain can display different pharmacologic properties even within the same receptor subtype (Fagg and Massieu, 1991).

The NMDA receptor appears to be concentrated primarily in the limbic system and is therefore very important to function in the limbic cortex, anterior cingulate, hippocampus, and ultimately other areas of the human brain (Tamminga, 1999). Recently there has been growing recognition of the critical role that NMDA receptors play in a number of physiological processes, including synaptogenesis, long-term potentiation, learning, memory and modulation of motor function (Cotman et al., 1988; Reid and Morris, 1991). In addition to their role in human CNS functions, NMDA receptors have been implicated in the pathophysiology of Glu-associated excitatory brain processes (Olney, 1989; Whetsell and Shapira, 1993), and of neuropsychiatric disorders such as epilepsy, Huntington’s disease and Alzheimer’s disease (for review, see Thomas, 1995). Recent data also suggest a putative role of NMDA receptors in mood and some anxiety disorders (for review, see Heresco-Levy and Javitt, 1998a). NMDA receptor-mediated processes at the level of the amygdala may be critical for development of fear conditioning (Charney et al., 1993). In preclinical models of depression, functional antagonists of the NMDA receptor are as efficacious as clinically active antidepressants such as imipramine (Skolnick et al., 1992). Moreover, antidepressants drawn from every principal therapeutic class were shown to produce adaptive changes in NMDA receptor function (Nowak et al., 1993; Paul et al., 1994) consistent with the hypothesis that this receptor
complex may serve as a final common pathway of antidepressant action.

The NMDA receptor is a ligand-gated ion channel permeable to calcium as well as to monovalent cations that is also voltage-dependent and has slow gating kinetics. This type of receptor is probably the most structurally complex Glu receptor, due to the multiple modulatory sites that are located around the primary multimeric protein and can modify ion flow through the receptor channel (for review, see Cotman et al., 1988). The primary neurotransmitter recognition site of the NMDA receptor binds Glu, aspartate and NMDA. The other sites include: (i) a co-agonist site that binds glycine (Gly), (ii) a cation channel that allows calcium conduction, (iii) an inhibitory intra-channel site that binds PCP, ketamine, MK-801 and other non-competitive antagonists, (iv) a voltage-dependent site that binds magnesium and may block channel conductance, and (v) an allosteric modulatory site that recognizes polyamines. This structural complexity and relative abundance of modulatory sites suggest that the NMDA receptor represents an inherently rich target for the development of innovative pharmacological strategies and corresponding new drugs. Since direct-acting NMDA agonists are excitatory and potentially excitotoxic, the assessment of NMDA receptor-based treatments for schizophrenia has recently focused on the study of indirect-acting NMDA agonists.

**NMDA receptor glycine-site agonists**

The main NMDA receptor-based treatment approach that has been clinically investigated during the last decade is the enhancement of NMDA receptor-mediated neurotransmission via administration of compounds having full or partial agonist activity at the strychnine-insensitive Gly recognition site of the receptor. Acting at this site, Gly serves as an obligatory NMDA co-agonist (Johnson and Asher, 1987), the degree to which presynaptically released Glu stimulates NMDA receptor-mediated activity depending upon tonic Gly levels in the immediate vicinity of NMDA terminals. In rodents, systemic injections of PCP and other non-competitive NMDA antagonists induce a characteristic behavioural syndrome, including hyperactivity and stereotypies. This syndrome is sensitive to administration of Gly-site agonists including Gly, d-serine (DSR) and d-alanine (Contreras, 1990; Javitt et al., 1997; Tani et al., 1994; Toth and Lajtha, 1986) but not to administration of similar doses of a variety of other amino acids (Toth and Lajtha, 1986). In preclinical trials (Norris et al., 1992), the glycinergic prodrug milacemide was shown to potentiate the ability of MK-801 to antagonize electrically precipitated tonic hindlimb extension. Moreover, Deutsch et al. (1997, 1999) demonstrated that MK-801-elicited mouse popping behaviour can be influenced by conventional and atypical antipsychotics treatment as well as by the administration of the Gly site partial agonist d-cycloserine (DCS). These findings are consistent with the hypothesis advocating the use of a peripherally administered glycineric intervention in order to modulate NMDA receptor-mediated neurotransmission in the intact organism. Further support for the feasibility of this approach derives from the demonstration of high-affinity Gly type 1 (GlyT1) transporters that are co-localized with NMDA receptors (Liu et al., 1993; Smith et al., 1992; Zafra et al., 1995). These transporters may keep Gly levels low in the microvicinity of the NMDA complex (Supplisson and Bergman, 1997), permitting physiologic regulation of NMDA receptors by Gly (Wood, 1995) or compounds having similar pharmacological activity (Javitt et al., 1999). Based upon these concepts and the general theoretical framework of the PCP model of schizophrenia (Heresco-Levy et al., 1993), four compounds: milacemide, Gly, DSR and DCS, have been repeatedly assessed as potential treatments in samples of schizophrenia patients.

**Milacemide**

Milacemide, an amino acetamide derivative that has been extensively studied in humans as a potential antiepileptic and cognition enhancer, increases Gly levels in CNS by dissociating into Gly-amide and then Gly, after passing through the blood–brain barrier (DeVarbeke et al., 1988). In rats, after milacemide administration, whole-brain Gly levels increase by approx. 30%. Milacemide, which was eventually withdrawn from use due to hepatotoxicity unrelated to its CNS effects, was found to be capable of reversing discriminative stimulus effects of PCP and of enhancing cognition in various animal (Finkelstein et al., 1994; Handelmann et al., 1989; Quartermain et al., 1990) and human (Schwartz et al., 1991) models, consistent with its ability to potentiate NMDA receptor neurotransmission via metabolism to Gly.

However, Tamminga et al. (1992) did not find milacemide to have any antipsychotic effects in a double-blind, placebo-controlled, cross-over study with 1200 mg/d p.o. milacemide in schizophrenia patients; no effects on mental status or side-effects being registered. The several patients tested in this study were otherwise drug free, and in a stable yet psychotic clinical state. Similarly, Rosse et al. (1991) reported a negative study using low-dose milacemide as add-on therapy with neuroleptics-treated schizophrenia patients. The negative results of these two preliminary studies could be due to small number of patients studied and/or to the low potency of milacemide. Furthermore, it should be taken
into account that milacemide affects additional neurotransmitter systems as well. For example, it also increases central serotonin and dopamine levels by inhibiting the action of monoamine oxidase type A, is an inhibitor as well as a substrate for monoamine oxidase type B, and blocks bicuculline-induced convulsions, suggesting a role for GABA in its mechanism of action (Semba et al., 1992; Yousim, 1991). These findings raise doubts regarding the role of the Gly site as the specific, primary site of action of this drug.

**Glycine**

Glycine is a small, neutral amino acid that constitutes 1–5% of dietary protein (McGeer et al., 1978). Almost all Gly in the brain is derived from the cleavage of serine by serine hydroxymethyl transferase (SHMT). With tetrahydrofolate as a co-factor, SHMT catalyses the interconversion of serine and Gly. Additional Gly may also be derived from the demethylation of sarcosine in the intramitochondrial matrix. In the spinal cord and brainstem Gly acts as an inhibitory neurotransmitter at a strychnine-sensitive site. By contrast, in the prefrontal cortex, Gly is one of the most potent agonists known to act at the strychnine-insensitive Gly site associated with the NMDA receptor. Its co-agonist action at this site positively modulates NMDA receptor function by increasing the frequency of NMDA ionophore opening and by delaying NMDA receptor desensitization (for review, see D’Souza et al., 1995). Permeation of Gly into brain following peripheral administration is the lowest of any naturally occurring amino acid (Oldendorph, 1971) and large peripheral doses of Gly must be administered in order to obtain modest elevations in CNS levels. Despite the poor permeation into CNS, Gly treatment may nevertheless be effective in that even relatively modest increases in CNS Gly levels may be sufficient for potentiating NMDA receptor-mediated neurotransmission (Heresco-Levy et al., 1996a).

To date, the results of the first 10 open-label and controlled studies investigating the therapeutic potential of various adjuvant Gly regimens in a total of approx. 140 schizophrenia patients are available (Table 1). The earliest study with Gly (Waziri, 1988) was performed before the relationship between Gly and NMDA function was fully appreciated. That study was based on the observation that schizophrenia subjects had lower SHMT activity than controls. Since SHMT activity is the major source of Gly in the brain, it was postulated that schizophrenia may be associated with decreased CNS Gly levels. Subsequent studies had not found decreased CSF Gly (Korpi et al., 1987; Perry and Hansen, 1985) or Glu (Gattaz et al., 1985; Macciardi et al., 1990) levels in schizophrenia. Nevertheless, in the study of Waziri (1988), 11 subjects were administered Gly doses of 5–25 g/d, in a naturalistic, open fashion over the course of months, during which time their neuroleptic regimen was gradually reduced or discontinued. Four patients were noted to show “definite salutary response” as indicated by decreased need for neuroleptics and improved social/vocational functioning, whereas the remaining patients did not ameliorate. Two patients were able to tolerate remaining free of neuroleptics for 7 and 8 months, respectively. Subsequently, as interest in NMDA receptor-mediated neurotransmission increased (Deutsch et al., 1989; Javitt, 1987; Olney, 1989), several additional studies were performed with Gly doses of up to 30 g/d (approx. 0.4 g/kg body weight). The first controlled Gly trial (Potkin et al., 1992) which used a Gly dose of 15 g/d, demonstrated significant global improvement following Gly treatment and a trend toward improvement on the Brief Psychiatric Rating Scale (BPRS). In a subsequent controlled study, using an increased adjuvant Gly dose of approx. 30 g/d, Javitt et al. (1994) found a significant 17% mean reduction in negative symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS), in a sample of neuroleptic-treated chronic schizophrenia patients. In contrast, in two controlled studies, no therapeutic effects were registered when 30 g/d (Potkin et al., 1999) and 60 g/d Gly (Evins et al., 2000) were added to the drug regimen of clozapine-treated patients.

Recently, Heresco-Levy et al. (1996b, 1999a) reported the results of a 6-wk, double-blind, placebo-controlled, cross-over trial in which 0.8 g/kg d Gly – the highest Gly dose used to date in schizophrenia – were added to the antipsychotic regimen received by in-patients fulfilling treatment-resistance criteria. Symptoms were assessed bi-weekly throughout the study, using the BPRS and a 5-factor PANSS model (Lindemayer et al., 1994) dividing symptoms into clusters labelled positive, negative, cognitive, depression and excitement. A significant (p < 0.001) 30% mean reduction in total BPRS scores was observed during treatment with Gly but not placebo. Gly treatment led to a 30% (p < 0.001) mean decline in negative symptoms, as measured by the PANSS, whereas no significant change in negative symptoms was observed during placebo treatment. Cognitive and depression symptoms also improved significantly (p < 0.01) by 16 and 17%, respectively, during treatment with Gly but not placebo. The treatment × time interaction remained significant for negative and cognitive symptoms even following covariance for changes in depression and extrapyramidal symptom scores. On the individual item level, highly significant improvement (p < 0.001) was observed on all items included in the PANSS 5-factor negative symptom cluster, as well as in additional items considered negative symptoms in the original 3-factor (i.e.
Table 1. Clinical trials with glycine (Gly) in the treatment of schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Design</th>
<th>Sample duration (wk)</th>
<th>Antipsychotic treatment</th>
<th>Daily Gly dose (g)</th>
<th>Symptoms* measures</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waziri (1988)</td>
<td>11</td>
<td>Open label, naturalistic</td>
<td>36</td>
<td>Varied</td>
<td>5–25</td>
<td>Not specified</td>
<td>35% improved; neuroleptic treatment reduced or withdrawn</td>
</tr>
<tr>
<td>Rosse et al. (1989)</td>
<td>8</td>
<td>Open label</td>
<td>≤ 8</td>
<td>Varied</td>
<td>10.8</td>
<td>BPRS, SANS, CGI</td>
<td>33% improved BPRS, 33% worsened BPRS</td>
</tr>
<tr>
<td>Costa et al. (1990)</td>
<td>6</td>
<td>Open label</td>
<td>6</td>
<td>Varied</td>
<td>15</td>
<td>BPRS: &gt; 30% improvement</td>
<td>33% improved</td>
</tr>
<tr>
<td>Heh et al. (1992)</td>
<td>8</td>
<td>Open label</td>
<td>≤ 5</td>
<td>Drug-free</td>
<td>≤ 20</td>
<td>BPRS: &gt; 30% improvement</td>
<td>No therapeutic effects</td>
</tr>
<tr>
<td>Potkin et al. (1992)</td>
<td>18</td>
<td>Double-blind, placebo-controlled</td>
<td>6</td>
<td>Varied</td>
<td>15</td>
<td>BPRS: &gt; 30% improvement</td>
<td>Trend towards improvement with Gly (20% improved, &gt; 30% in BPRS)</td>
</tr>
<tr>
<td>Javitt et al. (1994)</td>
<td>14</td>
<td>Double-blind, placebo-controlled followed by open label</td>
<td>8 blind</td>
<td>Varied</td>
<td>30</td>
<td>BPRS, SANS, CGI</td>
<td>17% improvement in negative symptoms</td>
</tr>
<tr>
<td>Leiderman et al. (1996)</td>
<td>5</td>
<td>Open label</td>
<td>8</td>
<td>Varied</td>
<td>60</td>
<td>SANS, PANSS</td>
<td>Significant SANS improvement</td>
</tr>
<tr>
<td>Potkin et al. (1999)</td>
<td>19</td>
<td>Double-blind, placebo-controlled</td>
<td>12</td>
<td>Clozapine</td>
<td>30</td>
<td>BPRS, SANS, PANSS</td>
<td>No therapeutic effects</td>
</tr>
<tr>
<td>Heresco-Levy et al. (1996b, 1999a)</td>
<td>22</td>
<td>Double-blind, placebo-controlled, cross-over</td>
<td>6</td>
<td>Varied</td>
<td>60</td>
<td>BPRS, SANS, PANSS</td>
<td>30% improvement in negative symptoms</td>
</tr>
<tr>
<td>Evins et al. (2000)</td>
<td>30</td>
<td>Double-blind, placebo-controlled</td>
<td>8</td>
<td>Clozapine</td>
<td>60</td>
<td>BPRS, SANS, PANSS</td>
<td>No therapeutic effects</td>
</tr>
</tbody>
</table>

* BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; SANS, Schedule for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale.
Table 2. Positive and Negative Syndrome Scale (PANSS) item reduction during 0.8 g/kg/day Gly treatment by significance level

<table>
<thead>
<tr>
<th>Item (Symptom Cluster)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>p &lt; 0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Blunted affect (N, N)</td>
<td></td>
</tr>
<tr>
<td>Emotional withdrawal (N, N)</td>
<td></td>
</tr>
<tr>
<td>Poor rapport (N, N)</td>
<td></td>
</tr>
<tr>
<td>Passive/apathetic social withdrawal (N, N)</td>
<td></td>
</tr>
<tr>
<td>Difficulty in abstract thinking (N, C)</td>
<td></td>
</tr>
<tr>
<td>Lack of spontaneity and flow of conversation (N, N)</td>
<td></td>
</tr>
<tr>
<td>Stereotyped thinking (N, O)</td>
<td></td>
</tr>
<tr>
<td>Mannerisms and posturing (G, C)</td>
<td></td>
</tr>
<tr>
<td>Motor retardation (G, O)</td>
<td></td>
</tr>
<tr>
<td>Poor attention (G, C)</td>
<td></td>
</tr>
<tr>
<td>Lack of judgement and insight (G, O)</td>
<td></td>
</tr>
<tr>
<td>Active social avoidance (G, N)</td>
<td></td>
</tr>
<tr>
<td><strong>p &lt; 0.01</strong></td>
<td></td>
</tr>
<tr>
<td>Excitement (P, E)</td>
<td></td>
</tr>
<tr>
<td>Grandiosity (P, P)</td>
<td></td>
</tr>
<tr>
<td>Anxiety (G, D)</td>
<td></td>
</tr>
<tr>
<td>Disturbance of volition (G, O)</td>
<td></td>
</tr>
<tr>
<td>Depression (G, D)</td>
<td></td>
</tr>
<tr>
<td>Uncooperativeness (G, O)</td>
<td></td>
</tr>
<tr>
<td><strong>p &lt; 0.05</strong></td>
<td></td>
</tr>
<tr>
<td>Conceptual disorganization (P, C)</td>
<td></td>
</tr>
<tr>
<td>Guilt feelings (G, D)</td>
<td></td>
</tr>
<tr>
<td>Poor impulse control (G, E)</td>
<td></td>
</tr>
<tr>
<td>Suspiciousness/persecution (P, P)</td>
<td></td>
</tr>
<tr>
<td>Unusual thought content (G, P)</td>
<td></td>
</tr>
<tr>
<td>Preoccupation (G, D)</td>
<td></td>
</tr>
<tr>
<td><strong>No significant change</strong></td>
<td></td>
</tr>
<tr>
<td>Delusions (P, P)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations (P, O)</td>
<td></td>
</tr>
<tr>
<td>Hostility (P, E)</td>
<td></td>
</tr>
<tr>
<td>Somatic concern (G, D)</td>
<td></td>
</tr>
<tr>
<td>Tension (G, E)</td>
<td></td>
</tr>
<tr>
<td>Disorientation (G, C)</td>
<td></td>
</tr>
</tbody>
</table>

Three-factor modela; five-factor modelb.

a,b N, negative; a,b P, positive; G, general psychopathology; E, excitement; C, cognitive; D, depression and O, other item, not in five-factor model.

positive, negative, general psychopathology) PANSS model (Table 2). Highly significant improvements were also observed on items considered to belong to the cognitive symptom cluster, including difficulty in abstract thinking and poor attention. Among positive symptoms, improvement was observed in grandiosity, suspiciousness/persecution and unusual thought content; however, no change was observed in delusion, hallucinations and hostility. Overall, 24 of the 30 PANSS symptom items showed significant improvement during Gly treatment. In contrast, there was no significant change in any item during placebo treatment.

In this study, trough serum amino acids levels were obtained from all subjects at baseline and at the end of the 6-wk Gly and placebo treatment phases. Gly treatment led to significant (p < 0.001) 3.5-fold increase in serum Gly levels and low pretreatment Gly levels significantly (r = 0.80) predicted clinical response. Serine levels also increased significantly during Gly treatment and a significant (p < 0.072) correlation was observed between Gly and serine levels across subjects at the end of Gly treatment.

These findings provide initial support for the hypotheses that: (a) Gly may be effective for the treatment of primary negative symptoms of schizophrenia and (b) patients with consistently low serum Gly and serine levels may be the population of choice for treatment with Gly-site agonists. Overall, a number of published studies suggest a therapeutic effect of Gly in treatment-resistant schizophrenia and/or on negative symptoms (Table 1). The reported effects are weaker in lower dose studies (usually uncontrolled). However, at ≥ 30 g/d, significant negative symptoms reductions were consistently registered following adjuvant Gly treatment.

D-serine

DSR acts as an endogenous full agonist at the NMDA receptor-associated Gly site (for review, see Hashimoto and Oka, 1997) and can selectively block PCP-induced hyperactivity and stereotypy behaviour. Overloading of Gly can increase DSR in the brain through the Gly cleavage system; conversely, DSR can be converted sequentially to L-serine and Gly by racemase and SHMT. DSR has the advantage of being more permeable than Gly at the blood–brain barrier, thus requiring a reduced amount per dose. On the other hand, a specific concern with DSR is that large doses (i.e. 800 mg/kg) were reported to cause reversible acute tubular necrosis in animals (Carone et al., 1985).

To date, two studies assessing DSR as an add-on agent to other antipsychotics in schizophrenia treatment have
DSR treatment revealed significant mean reductions, 21% (p = 0.0004), 17% (p = 0.001) and 12% (p = 0.0008) respectively, in their negative, positive and cognitive symptoms, as measured by the PANSS. The cognitive enhancing effect was supported by the finding that subjects who received DSR treatment also improved their performance in the Wisconsin Card Sort Test (WCST), by achieving 0.9 more category at the end of the study (p = 0.02) DSR levels at weeks 4 and 6 correlated with symptom changes, higher serum levels being associated with more symptom improvements. Overall, DSR treatment was well tolerated and no significant side-effects were noted. Given the observed effect on positive symptoms registered in this study, it has been suggested (Krystal and D’Souza, 1998; Tsai et al., 1998) that DSR may represent the drug of choice for a Gly-site agonist monotherapy trial in schizophrenia. Nevertheless, in a methodologically identical study (Tsai et al., 1999a), similarly to results registered with Gly treatment, no significant symptom changes were registered when the same DSR dose (i.e. 30 mg/kg ∙ d) was added to clozapine treatment.

**D-Cycloserine**

Unlike Gly, the antituberculosis drug DCS (D-4-amino-3-isoxazolidone, seromycin) readily crosses the blood–brain barrier and acts as a relatively selective partial agonist at the Gly site for a narrow range of concentrations (Thompson et al., 1992; Watson et al., 1990). Potentially beneficial DCS psychotropic effects were first reported four decades ago, when 500–1000 g/d DCS were routinely used as part of multidrug antituberculosis regimens. Some mentally debilitated tuberculosis patients responded to DCS treatment with significant mental improvement, prompt increase of appetite and a sense of wellbeing bordering on euphoria, which could not be considered secondary to improvement in tuberculosis symptomatology (Epstein et al., 1959; Kendig et al., 1956). Crane (1961) administered 500 mg/d DCS to 30 tuberculosis patients suffering from various, mainly neurotic, mental disturbances and reported an overall improvement of mental condition in 47% of patients. However, administration of 500–3000 mg/d DCS in a naturalistic study, to 9 drug-free schizophrenia patients resulted mainly in exacerbation of psychotic symptoms, psychomotor agitation, confusion and mood alterations (Simeon et al., 1970).

The discovery of DCS physiological impact at the NMDA receptor, led, during the last decade, to renewed interest in DCS-induced psychotropic effects. In one controlled study (Schwartz et al., 1996) significantly enhanced implicit memory performance was registered following 15 mg/d DCS treatment in patients with probable Alzheimer’s disease of mild to moderate severity. For patients with schizophrenia, initial trials have attempted to define the DCS dose range over which adjuvant treatment with this compound may be beneficial (Table 3). DCS regimens of ≤ 30 mg/d were ineffective (Rosse et al., 1996), while dosages of ≥ 100 mg/d led to positive symptoms exacerbations (Casella et al., 1994; van Berckel et al., 1999) in two single-blind, dose-escalation trials, only a 50 mg/d DCS regimen led to significant improvements in negative symptoms when administered to typical neuroleptics (Goff et al., 1995), but not to clozapine-maintained (Goff et al., 1996) patients. Serum glutamate concentrations at baseline and the change in Gly concentrations significantly correlated with response of negative symptoms. In a mixed sample of conventional neuroleptic- and clozapine-treated patients (Heresco-Levy et al., 1998b), the negative symptoms improvement induced by 50 mg/d adjuvant DCS correlated with Gly baseline levels but was not significant vs. placebo.

Recently, Goff et al. (1999a,b) replicated the findings of their preliminary dose-finding trials in two double-blind, placebo-controlled studies. Addition of 50 mg/d DCS to clozapine led to significant negative symptoms worsening, compared to placebo (Goff et al., 1999b). In contrast, the addition of the same DCS regimen to typical neuroleptics resulted in improved negative symptoms (Goff et al., 1999a). In this study, 47 patients with schizophrenia meeting criteria for the deficit syndrome were randomized to DCS, 50 mg/d or placebo, added to their conventional neuroleptics for an 8-wk, double-blind trial. The mean 23% (p < 0.001) reduction in negative symptoms registered with DCS was significantly greater than the mean 7% (p = 0.02) reduction registered with placebo, as calculated by slopes representing Scale for the Assessment of Negative Symptoms (SANS) total scores. The rate of reduction in total SANS scores in the DCS group remained significantly greater than for the placebo group after controlling for change in extrapyramidal, positive and depression symptoms. Improvement of negative symptoms was significantly predicted by low neuroleptic dose and low baseline SANS scores. No DCS effects were found on performance of cognitive tests and clinical response did not correlate with serum amino acid concentrations at baseline.

A 50 mg/d DCS adjuvant regimen has been recently assessed also in a sample of treatment-resistant schizophrenia patients receiving conventional neuroleptics,
Table 3. Clinical trials with d-cycloserine (DCS) in the treatment of schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Design</th>
<th>Sample duration (wk)</th>
<th>Antipsychotic treatment</th>
<th>Daily DCS dose (mg)</th>
<th>Symptoms* measures</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeon et al. (1970)</td>
<td>10</td>
<td>Open label</td>
<td>2–16</td>
<td>Drug-free</td>
<td>500–3000</td>
<td>Non-standardized BPRS, SANS, CGI</td>
<td>Psychosis exacerbation</td>
</tr>
<tr>
<td>Cascella et al. (1994)</td>
<td>7</td>
<td>Double-blind, placebo-controlled</td>
<td>6</td>
<td>Conventional neuroleptics</td>
<td>250</td>
<td>BPRS, SANS</td>
<td>Psychosis exacerbation, negative symptoms improved in 2 patients</td>
</tr>
<tr>
<td>Goff et al. (1995)</td>
<td>9</td>
<td>4 doses of DCS and placebo, single-blind</td>
<td>2 per dose</td>
<td>Conventional neuroleptics</td>
<td>5, 15, 50, 250</td>
<td>BPRS, SANS</td>
<td>Negative symptoms and SIRP reaction time improvement with 50 mg/d</td>
</tr>
<tr>
<td>Goff et al. (1996)</td>
<td>10</td>
<td>4 doses of DCS and placebo, single-blind</td>
<td>2 per dose</td>
<td>Clozapine</td>
<td>5, 15, 50, 250</td>
<td>BPRS, SANS</td>
<td>No therapeutic effects</td>
</tr>
<tr>
<td>Rosse et al. (1996)</td>
<td>13</td>
<td>2 doses of DCS, double-blind, placebo-controlled</td>
<td>4 per dose</td>
<td>Molindone</td>
<td>10, 30</td>
<td>BPRS, SANS, CGI</td>
<td>No therapeutic effects</td>
</tr>
<tr>
<td>van Berckel et al. (1996)</td>
<td>14</td>
<td>5 doses of DCS, single-blind</td>
<td>0.6 per dose</td>
<td>Drug free</td>
<td>15, 25, 50, 100, 250</td>
<td>CGI, PANSS</td>
<td>Negative symptoms, improvement with 100 mg/d</td>
</tr>
<tr>
<td>Heresco-Levy et al. (1998b)</td>
<td>9</td>
<td>Double-blind, placebo-controlled, cross-over</td>
<td>6</td>
<td>Varied</td>
<td>50</td>
<td>BPRS, PANSS</td>
<td>General psychopathology improvement, negative symptoms improvement – not significant vs. placebo</td>
</tr>
<tr>
<td>van Berckel et al. (1999)</td>
<td>26</td>
<td>Double-blind, placebo-controlled</td>
<td>8</td>
<td>Conventional neuroleptics</td>
<td>100</td>
<td>CGI, PANSS</td>
<td>Psychosis exacerbation</td>
</tr>
<tr>
<td>Goff et al. (1999a)</td>
<td>47</td>
<td>Double-blind, placebo-controlled</td>
<td>8</td>
<td>Conventional neuroleptics</td>
<td>50</td>
<td>PANSS, SANS, GAS, HAMD</td>
<td>Negative symptoms, improvement on SANS</td>
</tr>
<tr>
<td>Goff et al. (1999b)</td>
<td>17</td>
<td>Double-blind, placebo-controlled, cross-over</td>
<td>6</td>
<td>Clozapine</td>
<td>50</td>
<td>GAS, SANS, PANSS</td>
<td>Negative symptoms, worsening</td>
</tr>
<tr>
<td>Heresco-Levy et al. (1999b)</td>
<td>24</td>
<td>Double-blind, placebo-controlled, cross-over</td>
<td>6</td>
<td>Conventional neuroleptics, olanzapine, risperidone</td>
<td>50</td>
<td>BPRS, PANSS, HAMD</td>
<td>Negative symptoms, improvement on PANSS</td>
</tr>
</tbody>
</table>

* BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; SANS, Schedule for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; GAS, Global Assessment Scale; HAMD, Hamilton Depression Rating Scale; SIRP, Sternberg’s Item Recognition Paradigm.
olanzapine or risperidone (Heresco-Levy et al., 1999b). In this 6 wk, controlled, cross-over study, a significant ($p < 0.05$) moderate effect size treatment $\times$ time DCS therapeutic effect vs. placebo was observed for PANSS negative symptoms cluster and PANSS total score. DCS treatment resulted in a mean 15% reduction in negative symptoms ($p < 0.05$). The negative symptoms improvement did not differ between patients treated with conventional neuroleptics vs. risperidone and olanzapine and was not related to changes in other symptom clusters. Low pretreatment Gly and serine serum levels significantly predicted clinical response (Figure 1).

Similarly to the conclusions of recent Gly studies the results of DCS trials performed to date suggest that DCS adjuvant treatment may be effective against primary negative symptoms of schizophrenia, in particular among patients having low Gly, and possibly serine, serum levels. However, the therapeutic DCS dose range appears to be restricted around a regimen of approx. 50 mg/d. This limitation may be due to the partial agonist characteristics of DCS. As a partial agonist at the Gly site, producing 40–60% activity compared to Gly (Hanngren et al., 1961; Henderson et al., 1990; Watson et al., 1990), DCS acts as an agonist in the presence of low Gly concentrations and as an antagonist in the presence of high concentrations (Emmett et al., 1991). DCS effects are further determined by the relative concentrations of other endogenous ligands possessing varying degrees of agonist activity, such as serine and alanine, as well as the endogenous antagonist kynurenic acid. The therapeutic effect of DCS on negative symptoms is postulated to result from a relative agonist rather than antagonist effect at the Gly site, since robust improvement in negative symptoms is produced by high-dose treatment with the full agonist Gly. Nevertheless, even at the same DCS concentration, the DCS net effect may not be homogeneous across patients due to differences in the magnitude of concentration-dependent partial agonist activity.

**Other NMDA receptor-based treatments**

Preliminary findings suggest that, in addition to Gly, DSR and DCS, other psychotropic agents that may modulate NMDA receptor function via a variety of mechanisms could be beneficial in the treatment of psychosis and schizophrenia.

**D-$\alpha$-Alanine**

The number of identified pure and partial Gly-site agonists continues to grow (for review, see D’Souza et al., 1995). An additional potential full Gly-site agonist is the amino acid $\alpha$-alanine. $\alpha$-Alanine has a lower affinity for the Gly site than Gly or DSR and although there is evidence to suggest that it is actively transported into the CNS, its precise bioavailability and pharmacokinetics are yet to be determined. In animal models of psychosis, intra-ventricular administration of $\alpha$-alanine inhibits methamphetamine and PCP-induced hyperactivity (Hashimoto et al., 1991; Tani et al., 1991, 1994) and blocks PCP/MK-801-induced stereotypies and ataxia (Contreras, 1990). Recently the results of the first adjuvant $\alpha$-alanine trial in...
schizophrenia have been presented (Tsai et al., 1999b). In this 6-wk controlled study, d-alanine treatment resulted in mean 20, 15 and 12% reductions, respectively, in negative, positive and cognitive symptoms as measured by the PANSS. These significant improvements further support the hypothesis of NMDA system hypofunction in schizophrenia.

**Gly transport inhibitors**

A potential alternate strategy for enhancing NMDA-mediated neurotransmission is by the use of Gly uptake antagonists. The degree to which presynaptically released Glu stimulates NMDA receptor-mediated activity depends upon the tonic Gly levels in the immediate surrounding region. When NMDA-associated Gly-binding sites were first described, it was theorized that they were normally saturated due to high extracellular Gly levels in brain. The recent molecular and biochemical characterization of a class of Gly transporter proteins in brain (Liu et al., 1993; Smith et al., 1992) suggests, however, that Gly concentration in micro domains may be regulated by these transporters. Of these, the Gly transporter type 1 (GlyT1) is expressed primarily in glia and neurons of the neocortex and archicortex in association with regions of high NMDA expression (Zafra et al., 1995). GlyT1 may serve to maintain low intrasynaptic Gly levels specifically in the local region around NMDA receptors. Inhibition of GlyT1 transporters may thus lead to elevation of Gly levels in the immediate vicinity of NMDA receptors and augmentation of NMDA receptor-mediated neurotransmission without requiring administration of exogenous Gly. Support for this concept derives from a recent study (Supplisson and Bergman, 1997) in which co-expression of GlyT1 transporters with NMDA receptors in Xenopus oocytes led to significant inhibition of NMDA receptor responsiveness. Blockade of GlyT1 transporters would thus, theoretically, be expected to exert an opposite effect (for review, see Javitt et al., 1999). The use of Gly transport blockers to enhance NMDA receptor function would be analogous to the use of noradrenaline-serotonin reuptake inhibitors in order to enhance monoaminergic neurotransmission.

Gly transport antagonists suitable for clinical trials are not yet available. Nevertheless, the Gly derivative glycyldodecylamide (GDA) was found to be approx. 80-fold more potent than Gly in reversing PCP-induced hyperactivity (Toth et al., 1986), although, even large GDA doses did not significantly elevate whole-brain Gly levels. Recently, Javitt and Fruscianti (1997) have demonstrated that GDA acts as a selective Gly uptake antagonist at concentrations similar to those that would be obtained after peripheral administration. Furthermore, in animal behavioural studies, the potency of several novel GDA-related compounds for inhibiting PCP-induced hyperactivity in vivo correlated significantly with their potency in antagonizing Gly transport in vitro (Javitt et al., 1999). These findings suggest that Gly transport antagonists may induce similar effects to Gly and may therefore represent an appropriate alternative for targeted drug development.

**Antipsychotic drugs**

The efficacy of antipsychotic agents already in use in daily clinical practice may be related, at least in part, to their capacity to enhance NMDA receptor-mediated neurotransmission. Neuroleptics may upregulate NMDA receptor binding (Ulans and Cotman, 1993) and increase the expression of NMDA and non-NMDA Glu receptor subunits (Fitzgerald et al., 1995). Increases in the density of NMDA receptors bearing NR2B subunits would be predicted to enhance the efficacy of Gly because high-affinity Gly binding is limited to these NMDA receptors (Honer et al., 1998). Furthermore, recent studies have demonstrated that both haloperidol and clozapine may act similarly to partial agonists at the Gly site at concentrations approximating therapeutic levels (Banerjee et al., 1995; Fletcher and MacDonald, 1993). McCoy and Richfield (1996) also found that chronic administration of conventional and atypical antipsychotics produced a desensitization of the augmenting effect of Gly.

Several lines of investigation have implicated a glutamatergic mechanism of action for clozapine and possibly other atypical antipsychotics. Compared to conventional neuroleptics, clozapine treatment results in different patterns of Glu release and reuptake (Schneider et al., 1998; Yamamoto and Cooperman, 1994), potentiation of NMDA-mediated neurotransmission (Arvanov et al., 1997), reversal of PCP-induced isolative behaviour (Corbett et al., 1995), and deficits in sensorimotor gating (Bakshi et al., 1997). Clozapine is also quite potent in blocking NMDA receptor antagonist-induced neurotoxicity in the rat cerebral cortex (Farber et al., 1996) and it has recently been reported to block the exacerbation of ketamine-induced positive symptoms in schizophrenia patients (Malhotra et al., 1997b). Furthermore, no therapeutic effects have been registered to date in the studies that have examined the efficacy of Gly-site agonists used in conjunction with clozapine. The addition of Gly (Evins et al., 2000; Potkin et al., 1999) and d-serine (Tsai et al., 1999) to clozapine did not result in significant symptom changes, while the addition of 50 mg/d DCS to treatment with this drug has actually been reported to result in a worsening of negative symptoms (Goff et al., 1999b).
These findings have suggested the hypothesis (Goff et al., 1999b; Tsai et al., 1999) that the differential efficacy of Gly, DSR and DCS with non-clozapine- vs. clozapine-treated patients may be due to intrinsic agonist or partial agonist activity of clozapine at the Gly site, which may contribute to its unique clinical efficacy. Hence, the administration of Gly-site full agonists (i.e. Gly, DSR) to clozapine-treated patients could not further enhance NMDA-mediated neurotransmission, already influenced by clozapine, while DCS, in these circumstances, may have a Gly-site antagonist net effect leading to a worsening rather than an alleviation of symptoms. Presently, these hypotheses remain speculative, pending further clarification of the mechanisms responsible for antipsychotic activity, direct or indirect, at the NMDA receptor complex. Moreover, from both a theoretical and practical perspective, the systematic assessment of treatment regimens combining Gly-site agonists with other atypical antipsychotics, such as olanzapine and risperidone, is warranted.

Safety issues

Overall, in the studies performed to date, the administration of NMDA receptor-based treatments has been well tolerated by schizophrenia patients and no significant side-effects or alterations in clinical laboratory parameters have been registered.

Nevertheless, the main safety issue concerning the use of this type of agent remains neurotoxicity. In addition to its broad role in human brain function, glutamatergic neurotransmission may be involved in excitotoxic as well as chronic neurodegenerative brain disorders. Increased Glu release may actually augment the damage produced by stroke and hypoglycaemia and may actually cause dementia. In this context, concern has been expressed (Waziri, 1996) regarding the long-term safety of Gly-site agonists treatment in schizophrenia, based on the fact that excessive stimulation of NMDA receptors may lead to excitotoxic brain damage. In animals, elevated Gly levels appear to potentiate the excitotoxic effects of Glu or other NMDA agonists, although significant potentiating effects have been observed to date only when Gly levels are elevated many times above the physiological range (Globus et al., 1991) In schizophrenia, however, Glu levels appear to be either normal (Korpi et al., 1987) or reduced (Tsai et al., 1995) and studies that have specifically addressed the effects of Gly in the absence of increased Glu have concluded that ‘exposure of cortical neurons to Gly or DSR had very little effect on cell survival when added alone’ (Patel et al., 1990). Additional safety information regarding long-term treatment with Gly-site agonists derives from the fact that both milacemide and DCS have been through full FDA-approved trials and have been used with many thousands of patients without significant CNS toxicity being observed.

In order to examine possible Gly-induced neuronal and/or glial pathology, 2 controlled studies were recently performed in which rats were randomized to receive dietary supplementation with Gly. In the first study rats received 0.8 and 3.2 g/kg. d Glu for 2 wk (Shoham et al., 1999a); in a subsequent study rats received dietary supplementation with 1 and 5 g/kg. d Gly for 1, 3 and 5 months (Shoham et al., 1999b). Although these dietary regimens resulted in significant, dose-dependent Gly level increases, extensive morphological and immunohistochemical examination did not reveal any evidence of neurotoxic damage at any of the treatment intervals studied.

An additional drawback that may be associated with the use of some NMDA receptor modulators is due to the fact that the net physiological effect of Gly-site partial agonists may be heterogeneous across patients, depending upon individual characteristics and differences in relative concentrations of endogenous agonists and antagonists acting at the NMDA receptor complex. In such circumstances the administration of a partial agonist (e.g. DCS) may result, in some patients, in decreased NMDA receptor function and symptoms worsening. In 2 controlled studies performed to date with a 50 mg/d DCS dose added to non-clozapine antipsychotic regimens (Goff et al., 1999a; Heresco-Levy et al., 1999b), a minority of patients (i.e. approx. 10%) underwent an apparent DCS-induced psychotic exacerbation. This type of outcome is consistent with earlier observations with higher adjuvant DCS regimens (Cascella et al., 1994; Simeon et al., 1970; van Berckel et al., 1999) and suggests that DCS and possibly other Gly-site partial agonists may pose a risk of positive symptoms exacerbation even at low dosages.

Conclusions and future directions

The PCP model of schizophrenia, although already over 40 yr old (Luby et al., 1959), continues to pose an important challenge to basic and clinical neuroscience to build from the schizophrenomimetic effects of NMDA receptor antagonists toward treatment advances for patients suffering from schizophrenia. During the last decade there has been significant progress in assessing the therapeutic potential of NMDA receptor-based treatment approaches for this illness. This generation of pioneering small studies has focused on examining the clinical effects of Gly-site modulators, such as milacemide, Gly, DSR and DCS. Overall, the results of these preliminary clinical
studies targeting the NMDA receptor complex support the concept of a hypoglutamatergic hypothesis of schizophrenia and warrant further, larger-scale investigation.

Particularly encouraging have been the results obtained with high-dose Gly and DSR adjuvant treatments, which seem to lead to significant improvement in negative and possibly other types of symptoms in treatment-resistant patients. Furthermore, preliminary findings indicate that monitoring serum levels of relevant amino acids may help identify a subgroup of patients that may represent the population of choice for treatment with this type of agent. The aims of future studies to be performed in this field should include: (i) the assessment of Gly-site modulators as mono- vs. add-on therapy, (ii) the comparison of efficacies of full vs. partial agonists of the Gly site, and (iii) the assessment of clinical effects of these agents as adjunctive treatments added to conventional neuroleptics vs. widely used atypical antipsychotics such as risperidone and olanzapine. This last issue highlights the importance of better understanding the interactions between this group of drugs and the mechanism of action of atypical antipsychotics.

As the study of Gly, DSR and DCS is just beginning to bear fruit, additional NMDA receptor-based treatments are contemplated. Other partial and full agonists of the Gly site have been identified and are beginning to be assessed. Furthermore, recent receptor-binding and electrophysiological experiments suggest that the clinical efficacy of some presently available typical and atypical antipsychotics may derive, at least in part, from their partial agonist action at the NMDA receptor complex. An additional promising new step may be the development of Gly reuptake blockers suitable for clinical use. These compounds may constitute important clinical as well as research tools. Their potential advantage would be the capacity to increase synaptic Gly levels, obviating the concerns that agonists or antagonists may not significantly alter these levels.

The role of glutamatergic neurotransmission in the pathophysiology and therapeutics of schizophrenia is presently in process of conceptualization. These developments take place within the broader context of intense research focusing on the role of EAA systems in various brain functions as well as pathophysiological processes. After decades of relative neglect, the beginning of the 21st century will probably bring about the development of schizophrenia treatments based upon the pharmacological manipulation of glutamatergic neurotransmission. New drugs, acting on this system, will permit the implementation of novel pharmacological treatment strategies and will further stimulate innovative basic as well as clinical research in schizophrenia and other neuropsychiatric disorders.

Acknowledgements

Supported by grants from the Scottish Rite Benevolent Foundation’s Schizophrenia Research Program, NMY, and the National Alliance for Research on Schizophrenia and Depression, NY, USA (Dr. U. Heresco-Levy). Parts of this article have won the 1998 Clinical Research Award of the Israel Society for Biological Psychiatry.

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