European Neuropsychopharmacology (2008) **18**, 333–338

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Cerebrospinal fluid D-serine and glycine concentrations are unaltered and unaffected by olanzapine therapy in male schizophrenic patients

Sabine A. Fuchs [a,c,*,1], Martina M.J. De Barse [a,1], Floor E. Scheepers [b,2], Wiepke Cahn [b,2], Lambertus Dorland [a,1], Monique G. de Sain-van der Velden [a,1], Leo W.J. Klomp [a,1], Ruud Berger [a,1], René S. Kahn [b,2], Tom J. de Koning [c,3]

[a] *Department of Metabolic and Endocrine Diseases and Department of Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands*
[b] *Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands*
[c] *Department of Metabolic Diseases, University Medical Center Utrecht, Utrecht, The Netherlands*

Received 30 November 2007; accepted 20 December 2007

KEYWORDS
Schizophrenia;
D-Serine;
Glycine;
NMDA-receptor;
Olanzapine;
Cerebrospinal fluid

Abstract

N-Methyl D-aspartate (NMDA)-receptor hypofunction has been implicated in the pathophysiology of schizophrenia and D-serine and glycine add-on therapy to antipsychotics has shown beneficial effects in schizophrenic patients. Nevertheless, previous studies have not shown consistently altered D-serine concentrations in cerebrospinal fluid (CSF) of schizophrenic patients. To confirm and extend these results, CSF concentrations of both endogenous NMDA-receptor co-agonists D-serine and glycine and their common precursor L-serine were analyzed simultaneously in 17 healthy controls and 19 schizophrenic patients before and 6 weeks after daily olanzapine (10 mg) treatment. CSF D-serine, L-serine and glycine concentrations and their relative ratios were similar between schizophrenic patients and controls and no differences were observed before and after olanzapine therapy. Thus, the NMDA-receptor hypofunction hypothesis in schizophrenia is not explained by olanzapine therapy-dependent absolute or relative decreases in CSF D-serine and glycine concentrations in this series of male patients, thereby not providing convenient markers for the disorder.

* Corresponding author. Department of Metabolic and Endocrine Diseases, University Medical Center Utrecht, Postbox 85090, 3508 AB Utrecht, The Netherlands. Tel.: +31 887554003; fax: +31 887555350.
E-mail address: S.Fuchs@umcutrecht.nl (S.A. Fuchs).
[1] Tel.: +31 887554292; fax: +31 887554295.
[2] Tel.: +31 887556370; fax: +31 887555443.
[3] Tel.: +31 887554003; fax: +31 887555350.

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doi:10.1016/j.euroneuro.2007.12.002

1. Introduction

Schizophrenia is a serious psychiatric condition, affecting 0.5–1% of the general population (Goldner et al., 2002). It is characterized by positive symptoms (including hallucinations and delusions), negative symptoms (including blunted affect and emotional withdrawal) and cognitive symptoms. The pathophysiology remains elusive. Abnormal glutamatergic neurotransmission through *N*-methyl D-aspartate (NMDA)-receptors might be involved, as NMDA-receptor antagonists induce schizophrenia-like psychoses in healthy individuals and exacerbate psychotic symptoms in schizophrenics (Lahti et al., 2001). In addition, some effective antipsychotic drugs, such as clozapine, potentiate NMDA-receptor mediated neurotransmission (Arvanov et al., 1997) and increase glutamate concentrations in serum (Goff et al., 1996; Evins et al., 1997) and specific brain areas (Daly and Moghaddam, 1993; Yamamoto and Cooperman, 1994). Both clozapine (Olney and Farber, 1994) and olanzapine (Farber et al., 1996) block NMDA-receptor antagonist-induced neurotoxicity, suggesting that these atypical antipsychotics share glutamatergic properties (Heresco-Levy, 2003). Furthermore, mutant mice with absent or reduced expression of NMDA-receptor subunits, display behavioral abnormalities similar to those observed in pharmacologically-induced animal models of schizophrenia (Miyamoto et al., 2001; Mohn et al., 1999). Finally, a number of genetic schizophrenia susceptibility loci comprise genes with roles in NMDA-receptor function or glutamatergic neurotransmission (Harrison and Owen, 2003). Together, all these studies strongly imply contribution of NMDA-receptor dysfunction to the pathophysiology of schizophrenia, collectively referred to as the NMDA-receptor hypofunction hypothesis (Goff and Coyle, 2001).

NMDA-receptors require simultaneous binding by glutamate and one of the endogenous co-agonists D-serine or glycine for activation. D-Serine and glycine add-on treatment to antipsychotics induces beneficial effects especially on negative symptoms of schizophrenia (Tuominen et al., 2006). Therefore, it was hypothesized that altered concentrations of these obligatory NMDA-receptor co-agonists contribute to NMDA-receptor dysfunction in schizophrenia (Hashimoto et al., 2003; Kumashiro et al., 1995) and several studies have investigated cerebrospinal fluid (CSF) D-serine concentrations (Bendikov et al., 2007; Hashimoto et al., 2005). Despite reporting lowered D-serine to total serine ratio (Hashimoto et al., 2005) or

Table 1 Subject characteristics of the schizophrenic patients

Subject	Age [a]	D [b]	DOI [c]	Drugs [d]	PANSS [e]			CGI [f]		
	(years)		(years)		1	2	8	1	2	8
1	21.0	2	4	2a	35	44	41	4	4	4
2	30.2	2	4	3	47	46	28	5	5	3
3	22.0	1	0.1	3	43	39	28	5	4	3
4	20.7	1	1.3	1	35	35	31	4	4	3
5	26.1	1	3	2	40	30	32	4	4	3
6	27.2	2	2.5	0	52	40	37	6	6	4
7	32.1	1	2.5	1+3	31	39	32	4	4	3
8	40.8	1	6	2a	43	40	25	4	5	3
9	30.3	1	3	1	37	46	31	5	5	4
10	41.4	1	0.5	1+3	39	31	22	3	3	2
11	32.0	1	10	2b+4	64	64	48	6	6	5
12	37.6	1	6	0	58	43	43	6	6	5
13	24.1	1	0.5	2a	48	45	41	5	5	5
14	35.8	1	7	0	44	[g]	[g]	5	5	[g]
15	32.5	1	15.5	3	47	43	35	5	5	4
16	34.6	1	2.5	2a+4	44	38	25	5	5	3
17	39.6	2	15	1	50	57	35	6	6	4
18	49.5	1	13	0	46	46	37	5	5	4
19	28.6	1	3.5	0	56	48	[g]	6	6	[g]
Mean (SD) 1–13 [h]	29.7 (7.1)		3.3 (2.8)		44.0 (9.6)	41.7 (8.5)	33.8 (7.7)	4.7 (0.9)	4.7 (0.9)	3.6 (1.0)
Mean (SD) 1–19 [h]	31.9 (7.7)		5.3 (4.8)		45.2 (8.4)	43.0 (8.2)	33.6 (7.1)	4.9 (0.9)	4.9 (0.9)	3.6 (0.9)

[a] Age in years.
[b] D = diagnosis: 1 = schizophrenia, paranoid type; 2 = schizophrenia, disorganized type. No patient had any form of personality disorder.
[c] DOI = duration of illness in years.
[d] Drugs = drugs before study. 0 = none, 1 = typical antipsychotics, 2 = atypical antipsychotics (2a = risperidone, 2b = clozapine), 3 = benzodiazepines, 4 = SSRIs. The protocol required a wash-out period of 4 weeks for clozapine and 2 weeks for all other medication.
[e] PANSS = Positive and Negative Symptom Scale as evaluated by an experienced psychiatrist at visits 1, 2 and 8. Visit 1 = day of inclusion in the study (on former medication). Visit 2 = start of olanzapine therapy (after wash-out of former medication). Visit 8 = end of the 6 weeks olanzapine trial.
[f] CGI = clinical global impression, scored by an experienced psychiatrist at visits 1, 2 and 8. 1 = normal, not at all ill, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill patients.
[g] No evaluation was performed due to patient absence or altered drug dosage.
[h] Patients 1–13 were included for olanzapine studies. Since there were no suitable CSF samples after 6 weeks of olanzapine treatment, patients 14–19 were analyzed only for comparison with healthy subjects.