Psychopharmacology (2004) 177: 79–83
DOI 10.1007/s00213-004-1924-5

ORIGINAL INVESTIGATION

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Prediction of changes in memory performance by plasma homovanillic acid levels in clozapine-treated patients with schizophrenia

Received: 8 September 2003 / Accepted: 26 April 2004 / Published online: 4 June 2004

Abstract *Rationale:* Cognitive dysfunction in schizophrenia has been demonstrated to be dependent, in part, on dopaminergic activity. Clozapine has been found to improve some domains of cognition, including verbal memory, in patients with schizophrenia. *Objectives:* This study tested the hypothesis that plasma homovanillic acid (pHVA) levels, a peripheral measure of central dopaminergic activity, would predict the change in memory performance in patients with schizophrenia treated with clozapine. *Methods:* Twenty-seven male patients with schizophrenia received clozapine treatment for 6 weeks. Verbal list learning (VLL)-Delayed Recall (VLL-DR), a test of secondary verbal memory, was administered before and after clozapine treatment. Blood samples to measure pHVA levels were collected at baseline. *Results:* Baseline pHVA levels were negatively correlated with change in performance on VLL-DR; the lower baseline pHVA level was associated with greater improvement in performance on VLL-DR during treatment with clozapine. Baseline pHVA levels in subjects who showed improvement in verbal memory during clozapine treatment (n=13) were significantly lower than those in subjects whose memory performance did not improve (n=14). *Conclusions:* The results of this study indicate that baseline pHVA levels predict the ability of clozapine to improve memory performance in patients with schizophrenia.

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Keywords pHVA · Memory · Cognition · Clozapine · Dopamine · Schizophrenia

Introduction

The ability of clozapine to ameliorate specific types of cognitive impairment in schizophrenia has been reported (Hagger et al. 1993; Buchanan et al. 1994; Lee et al. 1994, 1999; Hoff et al. 1996; McGurk 1999; Potkin et al. 2001; Purdon et al. 2001). Among the domains of cognitive function, secondary verbal memory (learning and memory) has been demonstrated to be associated with better long-term outcome, including social and work function, in patients with schizophrenia (Meltzer et al. 1996; Green et al. 2000; McGurk and Meltzer 2000). The basis for this improvement has been suggested to be the ability of clozapine to increase the release of dopamine (DA) or acetylcholine (Ach) in prefrontal cortex (Kuroki et al. 1998; Meltzer and McGurk 1999; Ichikawa et al. 2002). There is extensive evidence that both DA and Ach influence cognition in men (Mann et al. 1983; Bridge et al. 1985; Amin et al. 1994; Meltzer 1999). The recent demonstration that the form of catechol-O-methyltransferase, an enzyme involved in the metabolism of DA, is related to working memory performance, as measured by the Wisconsin Card Sorting Test, in schizophrenia, provides further evidence for the role of DA in cognition in schizophrenia (Egan et al. 2001; Malhotra et al. 2002).

Plasma levels of homovanillic acid (pHVA), the major metabolite of DA, have been studied extensively in subjects with schizophrenia as a peripheral marker of central dopaminergic activity (Bacopoulas et al. 1979; Kendler et al. 1981, 1982; Koreen et al. 1994; Sumiyoshi et al. 1997b, 1999, 2000a; Zhang et al. 2001; see Friedhoff and Amin 1997 for review). Although the contribution of the central nervous system to peripheral pHVA concentrations has been reported to be no more than 35% (Kopin et al. 1988; Maas et al. 1988), pHVA levels have been suggested to be an indicator of several aspects of schizophrenia, including vulnerability to develop the

illness (Siever et al. 1991; Sumiyoshi et al. 2000b). Indeed, baseline (pretreatment) pHVA levels have been shown to be influenced by polymorphism of the genes encoding the DA-D_3 receptor or tyrosine hydroxylase, the synthesizing enzyme of DA, in delusional disorder (Morimoto et al. 2002). It is noteworthy that women have higher concentrations of pHVA compared to men, which may have confounded previous studies of pHVA in schizophrenia using a mixed population of male/female subjects (see Sumiyoshi et al. 1997b for review).

Several studies have focused on the relationship between dopaminergic activity and cognitive performance. Plasma HVA concentrations were reported to be positively correlated with performance on the Similarity Test, a measure of executive function in normal subjects (Amin et al. 1994). Furthermore, HVA levels in cerebrospinal fluid were positively correlated with performance on the paired associates test, a test of verbal memory, in patients with Parkinson's disease (Mann et al. 1983). We previously reported that pHVA levels are affected by acute mental stress in normal control subjects (Sumiyoshi et al. 1998), and predict performance on a test of information processing in subjects in the prodromal phase of schizophrenia (Sumiyoshi et al. 2000b). Thus, despite the fact that pHVA levels only partially reflect central dopaminergic function, they may reflect neural activity related to cognition, such as verbal memory. A recent rat study (Hefco et al. 2003) also suggested the specific relationship between performance on the test of long-term memory and DA activity in the central nervous system, by demonstrating that lesioning of the ventral tegmental area or substantia nigra worsened performance on the multi-trial passive avoidance test.

To our knowledge, no attempt has been made to relate pHVA with cognitive change during treatment with clozapine in patients with schizophrenia. Based on the considerations, discussed above, it is postulated that improvement in verbal learning and memory performance would be associated with low baseline pHVA levels in patients treated with clozapine. Therefore, an analysis was performed to determine if baseline pHVA levels predict the ability of clozapine to improve memory performance.

Materials and methods

Subjects

Subjects for this study were 27 male patients meeting DSM-III-R criteria for schizophrenia (APA 1987). Patients were interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime and Change (SADS-C) versions (Endicott and Spitzer 1978). A psychiatric and neuroleptic treatment history was obtained from the patient, informants, and medical records. Patients with current history of substance abuse or dependence, seizure or head injury were excluded from the study. Eligible patients had a complete physical examination. Standard laboratory testing was normal. This protocol was approved by the Institutional Review Board of University Hospitals of Cleveland. After complete description of the study to the subjects, written informed consent was obtained. The demographic data of the subjects are presented in Table 1. The mean (SD) of the psychopathology scores during the drug-free period, as assessed by the Brief Psychiatric Rating Scale, 18-item version (Overall and Gorham 1962) (0–6 scale), were 26.2 (14.1) for the Total score and 9.8 (6.2) for the Positive subscale score.

Physical exercise, high-monoamine diets, alcohol and caffeine were restricted from the entry point to the study (>24 h prior to the blood sampling) (Sumiyoshi et al. 1997a,b). No patient had received a depot neuroleptic for at least 6 weeks.

Drug treatment

In order to prevent adverse reactions due to the interaction between different medications, all patients underwent a 7–21 day washout period depending on their condition. During this period, an occasional low dose of benzodiazepines or chlorhydrate was given when necessary. Clozapine treatment was performed according to previous reports (Hasegawa et al. 1993; Sumiyoshi et al. 1997a). Patients received clozapine at a dose of 25 mg/day initially; this was usually increased by 25–50 mg every few days. The treating psychiatrists adjusted the dose to optimize improvement in psychopathology, while attempting to keep the side effects of the drug tolerable. No other psychotropic drugs were administered, other than occasional benzodiazepines and chloral hydrate during the early phase of treatment. Treatment with clozapine continued for 6 weeks.

Evaluation of verbal memory

Verbal memory was assessed using Verbal List Learning (VLL)-delayed recall (VLL-DR) (Kenny and Meltzer 1991; Sumiyoshi et al. 2003) by Master's level psychologists, who were not informed of pHVA data. Different versions of the same test were used at baseline and 6-week evaluation (Lee et al. 1999; Sumiyoshi et al. 2003).

Table 1 Demographic data of subjects. Values represent mean±SD; *pHVA* plasma homovanillic acid; *VLL-DR* Verbal List Learning-Delayed Recall

Age (yr)	33.4±6.4
Age at onset of illness (yr)	22.0±5.8
Clozapine dose at 6 weeks (mg/day)	321.7±194.6
Number of previous hospitalization	4.2±3.1
pHVA levels (pmol/ml)	40.4±15.2
Baseline VLL-DR	6.5±3.1

pHVA measurement

Plasma HVA analysis was performed according to our previous reports (Sumiyoshi et al. 1997a,b). Blood samples were obtained at 9:30–10:00 a.m., 60 min after insertion of an indwelling venous catheter following an overnight fast. Blood was collected on the day of clinical assessment. The baseline memory performance and pHVA levels were measured when the patients were drug-free. Plasma was separated by centrifugation and stored at −80°C until the free HVA levels were measured.

Plasma levels of HVA were measured by high-performance liquid chromatography based on previous reports (Sumiyoshi et al. 1997a,b). The coefficients of variation for within-day and between-day analyses of pHVA were 5.2 and 6.8%, respectively.

Statistical analysis

Changes in the VLL-DR score during treatment with clozapine were analyzed by two-tailed paired *t*-test. Regression analysis was conducted to predict the change in the VLL-DR scores from baseline pHVA levels. Subgroup comparisons of clinical measures (age, age at onset of illness, number of previous hospitalization, and the VLL-DR scores) were made using two-tailed *t*-test. Pearson's correlation coefficients were obtained to relate clinical measures. Effect sizes (ES) were calculated by the method of Cohen (1977). Data are expressed as mean (SD) unless otherwise specified. Significance was considered when *P*-value was <0.05.

Results

All subjects fulfilled the 6-week trial with clozapine. The mean (SD) VLL-DR scores at baseline and 6 weeks were 6.5 (3.1) and 6.4 (2.8), respectively. The result of *t*-test showed no significant change (t=−0.05, P=NS, ES=0.01) for the 27 subjects treated with clozapine. There was no relationship between length of drug-washout period and baseline pHVA (r=−0.25, P=NS). In fact, the drug-washout period for patients whose baseline pHVA levels were below the median did not differ from that for the subjects with an above median value of pHVA (t=−1.8, P=NS). No significant correlation was found between baseline pHVA levels versus the baseline BPRS Total (r=0.09, P=NS) or Positive (r=0.12, P=NS) score, or changes in these BPRS scores (r=0.18, P=NS and r=0.19, P=NS, respectively), nor was there a significant relationship between change in the performance on VLL-DR and change in the BPRS Total (r=−0.06, P=NS) or Positive (r=−0.02, P=NS) score.

There was a marginal positive correlation between baseline pHVA and verbal memory at baseline (r=0.33, P=0.09). The results of regression analysis indicated a significant negative correlation between baseline pHVA levels and the change in VLL-DR scores during treatment with clozapine (Fig. 1; F=7.05; df=1.25; P=0.01). Therefore, it was assumed that the baseline pHVA levels of the 14 subjects whose VLL-DR scores worsened (Fig. 1) [48.9 (16.5) pmol/ml] were higher that those of the rest of the subjects (n=13) whose memory performance improved or at least did not deteriorate [31.3 (9.0) pmol/ml]. In fact, the comparison of the baseline pHVA levels between these two groups by *t*-test yielded a significant difference (t=−3.48, P=0.002), with a large ES of 1.26 (Fig. 2). Age, age at onset of illness, or number of previous hospitalization did not differ between these subgroups (data not shown).

The pHVA data at 6 week were obtained from 18 subjects. The mean (SD) clozapine dose for these patients at 6 weeks was 358.3 (200.8). There was a 26% increase in pHVA levels [41.5 (16.9) versus 52.2 (28.2) pmol/ml] in these patients during treatment with clozapine. However, this change did not reach significance (t=−1.4, P=0.18). No significant association was observed between clozapine dose versus change in pHVA levels (r=0.23, P=NS), or change in the VLL-DR score (r=0.22, P=NS).

The score of VLL-Immediate Recall (VLL-IR) for all subjects at baseline and 6 week were 7.8 (2.2) and 7.3 (2.4), respectively. There was no significant correlation between baseline pHVA and the performance on VLL-IR at baseline or its change during clozapine treatment (data not shown).

Discussion

The results of this study suggest the first evidence that the baseline pHVA levels predicted the change in performance on verbal learning and memory, as measured by VLL-DR, in patients with schizophrenia treated with clozapine.

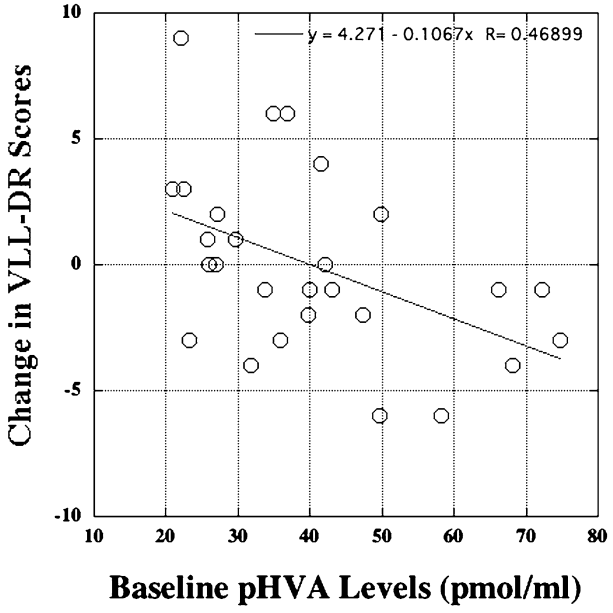

Fig. 1 Relationship between baseline pHVA levels and change in the VLL-DR scores (scores at 6 weeks−scores at baseline) in clozapine-treated patients with schizophrenia

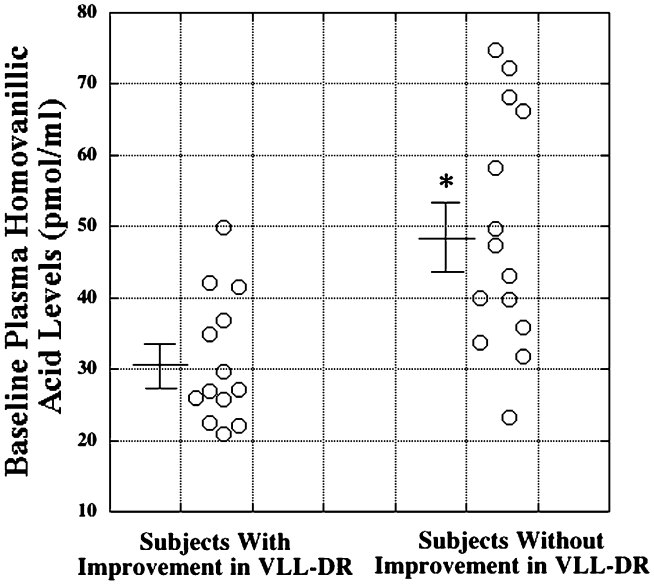

Fig. 2 Baseline pHVA levels in subjects who did or did not show improvement in the VLL-DR score during treatment with clozapine. *P=0.002, by two-tailed t-test

An association between dopaminergic activity, as reflected by pHVA levels, and cognitive abilities related to learning and memory in the patients who received clozapine, was suggested by the correlation between baseline pHVA levels and changes (6 week vs. baseline) in performance on VLL-DR. Preclinical and clinical studies suggest that subcortical structures, such as nucleus accumbens (NAC), constitute the major component of the brain HVA output (Csernansky et al. 1990; Lambert et al. 1991; Sumiyoshi et al. 2000a). There may also be a contribution of cortical DA neurons, as the ventral tegmentum is the source of the DA neurons projecting to both the cortex and NAC. Animal studies have found a role of dopaminergic transmissions in the ventral striatum for behaviors that require memory performance (Williams et al. 1993; Ploeger et al. 1994; Winnicka 1999; Hefco et al. 2003). For example, Ploeger et al. (1994) reported that intra-accumbens injections of haloperidol (a DA-D_2 blocker), at doses that do not affect motor function, impaired spatial learning in rats, suggesting an involvement of mesolimbic dopaminergic activity in some types of cognitive performance. Hefco et al. (2003) found impaired performance on behavioral measures of processing and storage of information in rats with neurotoxic lesions of the ventral tegmental area or substantia nigra. Based on the findings, they concluded that long-term memory is especially affected by decreased DA levels in some DA-rich brain areas. On the other hand, clozapine has been shown to increase the DA efflux in prefrontal cortex (Kuroki et al. 1998; Meltzer and McGurk 1999; Ichikawa et al. 2002). Therefore, it is possible that clozapine improves verbal memory in some patients with schizophrenia through modulation of dopaminergic transmissions in some brain areas regulating cognitive function.

The ability of pHVA to predict the degree of change in verbal memory during clozapine treatment may have important implications for clinical practice, as this domain of cognition is regarded as most relevant to social and occupational function in patients with schizophrenia (Meltzer et al. 1996; Green et al. 2000; McGurk and Meltzer 2000). Previous studies have generally reported that *high* baseline pHVA levels are associated with improvement of psychotic symptoms in subjects treated with typical or atypical antipsychotic drugs (see Sumiyoshi et al. 1997a for review). In this study, low baseline pHVA was associated with improvement of verbal memory during clozapine treatment. These discrepant findings may be explained by the fact that cognition and psychotic symptoms are two relatively independent domains of pathology in schizophrenia, as indicated by the lack of correlation between the scores of BPRS and VLL-DR in the subjects reported here. Investigations of the relationship between pHVA levels and the long-term outcome measures in patients treated with clozapine or other atypical antipsychotic drugs are warranted.

Acknowledgements This work was supported by a Fellowship and a Grant-in-Aid for Scientific Research (No. 16591126) from the Ministry of Education and Science of Japan, a Pharmacopsychiatry Research Grant from the Mitsubishi Pharma Research Foundation, and a Young Investigator Award from NARSAD to Dr. T. Sumiyoshi, as well as grants from the Warren Foundation, Mr. and Mrs Donald Test Jr, and Pharmacia to Dr. H.Y. Meltzer. We are grateful to Dr. Mitsuru Hasegawa and Mr. Jin Dai for technical assitance.

References

American Psychiatric Association (1987) DSM-III-R: diagnostic and statistical manual of mental disorders, 3rd revised edn. American Psychiatric Association, Washington D.C.

Amin F, Seeman TE, Mohs RC, Davidson M, Knott P, Berkman LF, Albert M, Blazer D (1994) Plasma homovanillic acid and performance on motor and cognitive tasks in community-dwelling elderly: MacArthur studies of successful aging. Neuropsychopharmacology 10:29–35

Bacopoulas NG, Hattox SE, Roth RH (1979) 3,4-Dihydroxyphenylacetic acid and homovanillic acid in rat plasma: possible indicators of central dopaminergic activity. Eur J Pharmacol 56:225–236

Bridge TP, Kleinman JE, Karoum F, Wyatt RJ (1985) Postmortem central catecholamines and antemortem cognitive impairment in elderly schizophrenics and controls. Neuropsychobiology 14:57–61

Buchanan RW, Holstein C, Breier A (1994) The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biol Psychiatry 36:717–725

Cohen J (1977) Statistical power analysis for the behavioral sciences, revised edn. Academic, New York

Csernansky JG, Barnes DE, Bellows EP, Lombrozo L (1990) Interrelationships between plasma homovanillic acid and indices of dopamine turnover in multiple brain areas during haloperidol and saline administration. Life Sci 46:707–713

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 98:6917–6922

Endicott J, Spitzer RL (1978) A diagnostic interview: the schedule for affective disorder and schizophrenia. Arch Gen Psychiatry 35:837–844

Friedhoff AJ, Amin F (1997) Plasma homovanillic acid in schizophrenia: implication for presynaptic dopamine dysfunction. American Psychiatric Association, Washington D.C.

Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 26:119–136

Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY (1993) Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biol Psychiatry 34:702–712

Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY (1993) Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 13:383–390

Hefco V, Yamada K, Hefco A, Hritcu L, Tiron A, Nabeshima T (2003) Role of the mesotelencephalic dopamine system in learning and memory process in the rat. Eur J Pharmacol 475:55–60

Hoff AL, Faustman WO, Wieneke M, Espinoza S, Costa M, Wolkowitz O, Csernansky JG (1996) The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic inpatients. Neuropsychopharmacology 15:361–369

Ichikawa J, Dai J, O'Laughlin IA, Fowler WL, Meltzer HY (2002) Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology 26:325–339

Kendler KS, Heninger GR, Roth RH (1981) Brain contribution to the haloperidol-induced increase in plasma homovanillic acid. Eur J Pharmacol 71:321–326

Kendler KS, Heninger GR, Roth RH (1982) Influence of dopamine agonists on plasma and brain levels of homovanillic acid. Life Sci 30:2063–2069

Kenny JT, Meltzer HY (1991) Attention and higher cortical functions in schizophrenia. J Neuropsychiatr Clin Neurosci 3:269–275

Kopin IJ, Bankiewicz KS, Harvey-White J (1988) Assessment of brain dopamine metabolism from plasma HVA and MHPG during debrisobuin treatment: validation in monkeys treated with MPTP. Neuropsychopharmacology 1:119–125

Koreen AR, Lieberman J, Alvir J, Mayerhoff D, Loebel A, Chakos M, Amin F, Copper T (1994) Plasma homovanillic acid levels in first-episode schizophrenia. Arch Gen Psychiatry 51:132–138

Kuroki H, Meltzer HY, Ichikawa J (1998) Effect of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontalcortex and nucleus accumbens. J Pharmacol Exp Ther 288:774–781

Lambert GW, Eisenhofer G, Cox HS, Horne M, Kalff V, Kelly M, Jennings GL, Esler MD (1991) Direct determination of homovanillic acid release from the human brain, an indicator of central dopaminergic activity. Life Sci 49:1061–1072

Lee MA, Thompson PA, Meltzer HY (1994) Effects of clozapine on cognitive function in schizophrenia. J Clin Psychiatry 55:82–87

Lee MA, Jayathilake K, Meltzer HY (1999) A comparison of the effect of clozapine with typical neuroleptics on cognitive function in neuroleptic-responsive schizophrenia. Schizophr Res 37:1–11

Maas JW, Contreras SA, Seleshi E, Bowden CL (1988) Dopamine metabolism and disposition in schizophrenic patients: studies using debrisoquin sulfate. Arch Gen Psychiatry 45:553–559

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D (2002) A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 159:652–654

Mann JJ, Stanley M, Kaplan RD, Sweeney J, Neophytides A (1983) Central catecholamine metabolism in vivo and the cognitive and motor deficits in Parkinson's disease. J Neurol Neurosurg Psychiatry 46:905–910

McGurk SR (1999) The effect of clozapine on cognitive functioning in schizophrenia. J Clin Psychiatry 60:24–29

McGurk SR, Meltzer HY (2000) The role of cognition in vocational functioning in schizophrenia. Schizophr Res 45:175–184

Meltzer HY (1999) Treatment of schizophrenia and spectrum disorders: pharmacotherapy, psychosocial treatments, and neurotransmitter interactions. Biol Psychiatry 46:1321–1327

Meltzer HY, McGurk SR (1999) The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 25:233–255

Meltzer HY, Thompson PA, Lee MA, Ranjan R (1996) Neuropsychologic deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. Neuropsychopharmacology 14:27S–33S

Morimoto K, Miyatake R, Nakamura M, Watanabe T, Hirao T, Suwaki H (2002) Delusional disorder: molecular genetic evidence for dopamine psychosis. Neuropsychopharmacology 26:794–801

Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812

Ploeger GE, Spruijt BM, Cools AR (1994) Spatial localization in the Morris water maze in rats: acquisition is affected by intra-accumbens injections of the dopaminergic antagonist haloperidol. Behav Neurosci 108:927–934

Potkin SG, Fleming K, Jin Y, Gulasekaram B (2001) Clozapine enhances neurocognition and clinical symptomatology more than standard neuroleptics. J Clin Psychopharmacol 21:479–483

Purdon SE, Labelle A, Boulay L (2001) Neuropsychological change in schizophrenia after 6 weeks of clozapine. Schizophr Res 48:57–67

Siever LJ, Amin F, Coccaro EF, Bernstein D, Kavoussi RJ, Kalus O, Horvath TB, Warne P, Davidson M, Davis KL (1991) Plasma homovanillic acid in schizotypal personality disorder. Am J Psychiatry 148:1246–1248

Sumiyoshi T, Hasegawa M, Jayathilake K, Meltzer HY (1997a) Prediction of short-term changes in symptom severity by baseline plasma homovanillic acid levels in schizophrenic patients receiving clozapine. Psychiatry Res 69:113–121

Sumiyoshi T, Hasegawa M, Jayathilake K, Meltzer HY (1997b) Sex differences in plasma homovanillic acid levels in schizophrenia and normal controls: relation to neuroleptic resistance. Biol Psychiatry 41:560–566

Sumiyoshi T, Yotsutsuji T, Kurachi M, Itoh H, Kurokawa K, Saitoh O (1998) Effect of mental stress on plasma homovanillic acid in healthy human subjects. Neuropsychopharmacology 19:70–73

Sumiyoshi T, Saitoh O, Yotsutsuji T, Itoh H, Kurokawa K, Kurachi M (1999) Differential effects of mental stress on plasma homovanillic acid in schizophrenia and normal controls. Neuropsychopharmacology 20:365–369

Sumiyoshi T, Kurachi M, Itoh H (2000a) Schizophrenia and plasma homovanillic acid in response to mental stress: methodological considerations. Neuropsychopharmacology 23:347–349

Sumiyoshi T, Kurachi M, Kurokawa K, Yotsutsuji T, Uehara T, Itoh H, Saitoh O (2000b) Plasma homovanillic acid in the prodromal phase of schizophrenia. Biol Psychiatry 47:428–433

Sumiyoshi T, Jayathilake K, Meltzer HY (2003) The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. Schizophr Res 59:7–16

Williams GV, Rolls ET, Leonard CM, Stern C (1993) Neuronal responses in the ventral striatum of the behaving macaque. Behav Brain Res 55:243–252

Winnicka MM (1999) Dopaminergic projection to the nucleus accumbens mediates the memory-enhancing effect of angiotensins in rats. Pharmacol Biochem Behav 62:625–630

Zhang ZJ, Peet M, Ramchand CN, Shah S, Reynolds GP (2001) Plasma homovanillic acid in untreated schizophrenia—relationship with symptomatology and sex. J Psychiatr Res 35:23–28