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Abnormal plasma monoamine metabolism in schizophrenia and its correlation with clinical responses to risperidone treatment

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ABSTRACT

Abnormalities in plasma monoamine metabolism reflect partly the illness of schizophrenia and sometimes the symptoms. Such studies have been repeatedly reported but have rarely taken both metabolites and parent amines or inter-amine activity ratios into account. In this study, the monoamines, their metabolites, turnovers and between-metabolite ratios in plasma were measured longitudinally in 32 schizophrenic patients treated with risperidone for 6 weeks, to examine possible biochemical alterations in schizophrenia, and to examine the association between treatment responses and psychopathology assessed according to the Positive and Negative Syndrome Scale (PANSS). The results showed lower level of plasma 3,4-dihydroxyphenylacetic acid (DOPAC) in relapsed versus first-episode schizophrenic patients, higher norepinephrine (NE) turnover rate (TR) in undifferentiated in comparison to paranoid schizophrenic patients and relatively higher metabolic activity of dopamine (DA) to serotonin (5-HT) in first-episode versus relapsed schizophrenic patients. Risperidone treatment induced a decrement of plasma DA levels and increments of plasma DOPAC and DA TR in the total group of schizophrenic patients. The turnover rate of 5-HT was was reduced in undifferentiated and relapsed subgroups of schizophrenic patients. The linkages between 5-HT TR, DA/NE relative activity and clinical symptomatology were also identified. These findings are consistent with an involvement of these systems in the pathogenesis of schizophrenia as well as in the responses to treatment, and the usefulness of certain biochemical indices as markers for subgrouping.

Introduction

Alterations in monoaminergic transmission have since long been hypothesised in the pathophysiology of schizophrenia (van Kammen and Kelley, 1991). In its original form, the hypothesis predominantly suggested that schizophrenia is due to abnormal activity of the dopaminergic (DA) system supported by the common anti-DA properties of antipsychotic medications (Moore et al., 1999). Recent extensions of the dopamine hypothesis of schizophrenia have highlighted the interactions with other monoamines as well as other neurotransmitters (Carlsson et al., 2001). Therefore, documenting evidence continues to be put forward for contributions from other dysfunctional monoamine systems such as the noradrenergic (NE: Yamamoto and Hornykiewicz, 2004) and serotonergic (5-HT: Geyer and Vollenweider, 2008) systems.

One way to examine the DA, NE and 5-HT systems in the brain is through measurements of the parent amines and their metabolites in body fluids including cerebrospinal fluid (CSF), plasma and urine. Instead of focussing on psychiatric disorders or diagnoses, research on monoamine neurotransmitters has tended to focus on symptoms and behaviours that cut across diagnostic boundaries and on responses to antipsychotic treatment, as abnormalities of neurotransmitters may be better understood as correlates of psychological states than as causes of them (Moncrieff, 2009). Although plasma monoamines and their metabolites are of both central and peripheral origin (Goldstein et al., 2003; Eldrup, 2004) and thus may be weak indicators of activity affecting the central nervous system (CNS), in controlled conditions they could reflect changes that occur in the brain (Konicki et al., 1991) either because the central contribution is sufficient to dominate a statistical relation to peripheral changes, or because the central and peripheral pools are affected in a correlative way under genetic

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control (Kaminski et al., 1990). Thus, their changes that are registered are strong enough to be relevant to the studies of neuroleptic response and clinical symptoms.

In spite of some negative reports (Galinowski et al., 1998; Yoshimura et al., 2000), changes in plasma homovanillic acid (HVA), a major circulating DA metabolite, have been associated with changes in the severity of schizophrenic symptoms during antipsychotic treatment and after withdrawal (Pickar, 1986; Davidson et al., 1991). Moreover, there is a consensus for elevated HVA levels to be correlated with the negative syndrome (Zhang et al., 2001) and fewer positive symptoms (Kim et al., 2000). Results are in conflict about whether HVA levels are higher (Nibuya et al., 1995) or lower (Thibaut et al., 1998) in the deficit versus non-deficit syndromes. With regard to more specific symptoms, increased HVA has been related to more anhedonia (Zhang et al., 2001) and less depression and hostility (Sharma et al., 1998). While severities of predominant negative symptoms (Pickar et al., 1990), positive and negative symptoms (Maas et al., 1993) as well as and disorientation (Markianos et al., 1992) have been correlated with high plasma levels of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), increases of NE and MHPG from low levels have also been related to a good treatment response (Breier et al., 1994; Nagamoto et al., 1999). Platelet or plasma serotonin 5-HT and its metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) are usually elevated in schizophrenic patients (Dursun et al., 2000; Oades et al., 2002; Mück-Seler et al., 2004), although the differences are not always significant (Markianos et al., 1992) and are even opposite in poor responders (Van der Heijden et al., 2004). Increased plasma 5-HT metabolism may reflect increased hostility (Markianos et al., 1992) and impulsivity (Dursun et al., 2000), and lower severities of autistic or depressive symptoms (Alfredsson and Wiesel, 1990). Even if the existence of relationships with symptom dimensions and plasma monoamine activity is recognised, the research problem of accurately disentangling the role of one biogenic amine from the others related to the pathophysiology and treatment of schizophrenia may be still described as mind boggling.

Inconsistent results are usually attributed to small sample sizes and different treatments, but especially to the heterogeneity of the illness. It has been remarked that studies comparing a group of subjects with schizophrenia with another group often report differences without clarifying whether the feature concerned related only to a subgroup of the patients (Carpenter et al., 1999). In this study, the plasma concentrations of DA, NE, 5-HT, and their respective metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), HVA, vanillylmandelic acid (VMA), MHPG and 5-HIAA in schizophrenic patients were simultaneously determined, and their correlations with symptom dimensions were examined longitudinally during a 6-week risperidone antipsychotic monotherapy. Further, to increase the potential sensitivity and stability of associations between neurotransmitter activity and symptoms, we focus on relationships of the metabolites of the three principal monoamines to their parent amine and to each other to access the turnovers and the relative activities between the monoaminergic systems. We hypothesized that: (1) treatment with risperidone would alter aberrant plasma monoamine metabolism in schizophrenia; (2) compared with these monoamines, turnovers and between-system ratios would be better related to the symptom dimensions and treatment response; and (3) some monoamine metabolic features apparently characterising the whole patient group would be largely attributable to a given subgroup.

2. Methods

2.1. Subjects

Using DSM-IV-TR criteria (American Psychiatry Association, 2000) were used to make a diagnosis of schizophrenia in 38 inpatients admitted consecutively to the Second Xiangya Hospital of Central South University. Diagnoses were made by experienced psychiatrists after conducting a Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P: First et al., 2002). Inclusion criteria were as follows: first-episode neuroleptic-naïve or relapsed neuroleptic-free schizophrenic inpatients with more than 1 month of washout (first-episode drug-naïve was defined as the first time a patient was hospitalised for psychiatric illness and never exposed to neuroleptics; relapsed neuroleptic-free was characterised as a patient suffering from a relapse after a symptom-free medication discontinuation interval); without alcohol or drug abuse/dependency, chronic use of any other medication and any major medical or neurological disorder that would affect the aim of this study; ages varying between 18 and 50 years; and from the same geographic region and of the same ethnic origin. Antipsychotic monotherapies with oral risperidone at a target dosage of 3–6 mg day^{-1} were initiated in all patients. The dose of risperidone was increased progressively and all the medications were stabilised at the target dose before week 3. For ethical reasons, alprazolam and benzhexol were allowed as adjunctive medications to treat anxiety and extrapyramidal side effects, respectively, when necessary. Once the symptomatic treatment was started, it would continue to the end of observation. Of the 38 inpatients who entered the study, six did not complete 6 weeks. Two (all belong to disorganised subtype) of them dropped out because of poor response and clinical worsening, and the remaining four (disorganised/undifferentiated/residual: 2/1/1) left the hospital before week 6 for economic reasons. In addition, the control group composed of 30 sex- and age-paired healthy volunteers was recruited from the same region, with no personal or family history of psychopathology, no serious medical illness, no history of head injury and no history of drug/alcohol abuse. The demographic and clinical characteristics of the subjects who fulfilled the study's entrance criteria are presented in Table 1 (for detailed information about individual patients, see supplemental Table 1). All subjects gave their written informed consent in a protocol approved by the Medical Ethics Committee of the Second Xiangya Hospital, Central South University.

2.2. Blood sampling, biochemical measurements and psychopathology assessments

All participants were on a low monoamine diet for at least 3 days and fasted overnight before blood sampling. Whole blood samples of patients were collected using sodium heparin vacutainer tubes at around 7:00 at baseline and at weeks 3 and 6. After immediate centrifugation at 4 °C for 10 min at 1200 *g*, plasma were isolated and stored at −80 °C until analysis. Plasma samples of healthy controls were collected only once, following the same procedure. Plasma concentrations of monoamines and their metabolites (DA, DOPAC, HVA, NE, VMA, MHPG, 5-HT and 5-HIAA) were measured by a liquid chromatography-mass spectroscopy/mass spectroscopy (LC-MS/MS) method using pre-column derivatisation with dansyl chloride (Cai et al., 2010). The (DOPAC + HVA)/DA and HVA/DA ratios were employed to estimate the DA turnover rate (TR), which were set as DA TR 1 and DA TR 2, respectively. The (VMA + MHPG)/NE and MHPG/NE ratios were respectively defined as NE TR 1 and NE TR 2 in a like manner. The 5-HIAA/5-HT ratio was used to evaluate 5-HT TR. Between-monoaminergic activities (BMAs) were calculated by the following between-metabolite ratios: (DOPAC + HVA)/(VMA + MHPG), HVA/MHPG, (DOPAC + HVA)/5-HIAA, HVA/5-HIAA, (VMA + MHPG)/5-HIAA and MHPG/

Table 1
Demographic and clinical characteristics of the subjects.

	Schizophrenia					Control
	Paranoid	Undifferentiated	First-episode	Relapsed	Total	
Number	9	23	11	21	32	30
Sex (Male/Female)	1/8	13/10	6/5	8/13	14/18	13/17
Age (years, mean ± S.D.))	34.1 ± 8.2	31.7 ± 10.3	27.6 ± 9.5	34.9 ± 9.0	32.4 ± 9.7	32.6 ± 9.7
Number of relapses (mean ± S.D.)	2.3 ± 1.1	1.6 ± 1.6	0	3.0 ± 0.9	1.8 ± 1.5	–
Duration of illness (years, mean ± S.D.)	9.0 ± 6.7	6.9 ± 8.3	0.8 ± 0.6	11.0 ± 7.5	7.5 ± 7.8	–
Dose of risperidone (mg/d, mean ± S.D.)	3.6 ± 0.5	3.6 ± 0.7	3.5 ± 0.5	3.6 ± 0.7	3.6 ± 0.7	–
Dose of alprazolam (mg/d, mean ± S.D.)	0.5 ± 0.4	0.3 ± 0.3	0.3 ± 0.3	0.4 ± 0.4	0.3 ± 0.4	–
Dose of benzhexol (mg/d, mean ± S.D.)	4.0 ± 1.7	2.9 ± 2.0	3.1 ± 2.1	3.2 ± 1.9	3.2 ± 2.0	–