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Dopamine Turnover in Schizophrenia Before and after Haloperidol Withdrawal

CSF, Plasma, and Urine Studies

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The dopamine hypotheses of schizophrenia and antipsychotic drug action suggest that the dopamine metabolite homovanillic acid (HVA) should change with drug withdrawal and change in clinical state. We designed a study of cerebrospinal fluid (CSF), plasma, and urinary HVA on and off haloperidol to examine the effects of drug withdrawal. CSF and plasma HVA samples were obtained in 72 healthy schizophrenic (DSM-III-R) males (age: 36 ± 7.4 years), before and after haloperidol withdrawal, which was after 6 weeks on placebo or sooner if they met specific criteria for relapse. We collected three 24-hour urine samples in 34 of these patients. In addition, CSF HVA was obtained in 24 well-screened age-matched male normal controls. HVA was measured with high-pressure liquid chromatography (HPLC). CSF HVA decreased significantly after drug withdrawal, particularly in those who met relapse criteria; drug-free CSF HVA levels were not significantly different from those of normals. Plasma HVA increased significantly after haloperidol withdrawal in relapsing patients, but not in clinically stable patients. Urinary HVA excretion decreased after withdrawal with decreased HVA clearance. We conclude that haloperidol withdrawal had a strong effect on dopamine turnover, whereas the patient's clinical state had only a weak central effect, without affecting total body production of HVA. Conceivably, dopamine involvement in schizophrenia reflects the failure of the homeostatic mechanisms that allow for integration of different functional brain components as needed. ***[Neuropsychopharmacology 15:75–86, 1996]***

KEY WORDS: *Homovanillic acid; Cerebrospinal fluid; Urine; Plasma; Schizophrenia; Haloperidol treatment; Drug withdrawal*

For decades increased dopamine activity has been considered the major etiologic factor of psychotic symptoms (Davis et al. 1991) an assumption based on the observation that antipsychotic drugs block dopaminergic receptors (Carlsson and Lindqvist 1963; van Rossum 1966; Randrup and Munkvad 1972). However, the initial conceptualization of psychosis as a hyperdopaminergic state was found to be too simplistic an explanation (van Kammen 1979; Davis et al. 1991). Moreover, other neurotransmitters, such as norepinephrine (van Kammen et al. 1989) and serotonin (van Kammen et al. 1995, in press), have been implicated in the relapse process.

The major dopamine metabolite in humans, homovanillic acid (HVA), has been extensively studied in relatively small patient samples without settling the issue as to whether an increase in central dopamine metabolism is reflected in cerebrospinal fluid (CSF), plasma (Amin et al. 1992; Kahn and Davidson 1993; Koreen et al. 1994), or urine (Contreras et al. 1987, 1988; Maas et al. 1979, 1993a, 1993b). In addition, HVA may appear as a byproduct of norepinephrine synthesis (Scheinin 1986; Kopin et al. 1988a; Lambert et al. 1994, 1993). CSF HVA levels in schizophrenic patients are reportedly not different from those of normal control subjects (Post et

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al. 1975; Nybäck et al. 1983; Pandey et al. 1987; Pickar et al. 1990; Maas et al. 1993a; Hsiao et al. 1993) although Lindström (1985) found lower CSF HVA values in chronic patients. In spite of a lack of difference compared to normals, relatively high CSF HVA values have been associated with relapse in premorbid well-functioning patients (Post et al. 1975), with paranoid patients (Rimon et al. 1971), and a positive family history of schizophrenia (Sedvall and Wode-Helgodt 1980), but lower values correlate with Schneiderian symptoms (Bowers 1973; Post et al. 1975) and poor prognosis (Bowers 1974). Recovered patients (Post et al. 1975) had lower values with longer duration of treatment.

Plasma HVA levels in schizophrenic patients have been reported to be lower in chronic patients (Davidson and Davis 1988), not significantly different in first-episode schizophrenic patients (Koreen et al. 1994), or higher in acutely ill patients (Maas et al. 1993a) than for healthy controls. Urinary HVA levels have been reported to be similar in acutely ill patients and controls (Maas et al. 1993a) or decreased in chronic patients (Karoum et al. 1987). Others (Maas et al. 1993a; Whelton et al. 1993) did not find a difference in urinary HVA output between controls and patients. Few studies have looked at both CSF and plasma HVA under changing clinical circumstances such as before and after drug treatment (Sharma et al. 1989, 1993); none have looked at HVA in all three compartments concurrently (Linnoila et al. 1988).

Because the changes in CSF and plasma values after drug withdrawal appear to go in opposite directions [i.e., CSF HVA declines and plasma HVA increases (Pickar 1988)], we examined the interaction effects of haloperidol withdrawal and changes in clinical state on HVA levels in the different body fluid compartments. To assess whether the observed changes are not just the result of changes in clinical state and in clearance between the different compartments (CSF, plasma), we also calculated renal HVA clearance and measured total HVA production (Contreras et al. 1987, 1988). To overcome other sources of variance in CSF (van Kammen and Sternberg 1980; Potter et al. 1984; Csernansky et al. 1988a; Doran et al. 1990; Koreen et al. 1994); plasma (Kendler et al. 1983, Davidson et al. 1987), and urinary HVA (Karoum et al. 1987), we standardized for time of day for blood draws and lumbar punctures (LPs), activity, diet, and gender. CSF HVA data of an early subset of these patients have been published in a previous study (van Kammen et al. 1989).

METHODS

Subjects

Seventy-two physically healthy male veterans with a DSM-III-R diagnosis of schizophrenia (Table 1 for demographics) entered the drug withdrawal study voluntarily, on the Schizophrenia Research Unit at the DVA Medical Center, Highland Drive, in Pittsburgh, PA, after signing an informed consent form. Staff discussed with patients extensively the risks of drug withdrawal and previous prodromes and relapses for assessment of prodromes. Where appropriate, the procedures and risks were discussed with significant others. Only patients who had been treated for at least 6 months with antipsychotic drugs and who had experienced at least two previous relapses were invited to participate. Those with risk of suicide or severe violence, based on past history, were excluded. Clinical appropriateness, informed consent, diagnosis and demographic data of each potential participant were reviewed prior to research participation by a consensus meeting of the clinical staff. The Investigational Review Board (IRB) monitored the informed consent process. If the patients were not treated with haloperidol, they were switched to this drug for at least 2 months prior to testing. If patients were on long-acting agents, oral haloperidol replacement was given for at least 2 months. Patients adhered to a low-monoamine, caffeine-restricted and alcohol-free diet. After signing informed consent, patients received haloperidol in unmarked capsules. Haloperidol dose changes were completed and antiparkinsonian agents were discontinued at least 2 weeks before the first LP (Table 1 for dosages). Following this LP, haloperidol was discontinued between 2 and 10 days and replaced overnight with placebo. A second LP was performed after 6 weeks of placebo treatment or when patients met criteria for relapse (mean 28.7 ± 12.1, range 14–58 days). These specific criteria consisted of a mean increase over 3 consecutive days of three points or more on the 15-point psychosis item of the Bunney-Hamburg rating scale (Bunney and Hamburg 1963) over the mean during the last week of drug treatment. Forty patients remained clinically stable and participated in the research procedures after 6 weeks of placebo, 32 patients met relapse criteria before the completion of this period. After the patients completed the protocol or dropped out, they received antipsychotic drug treatment as indi-

Table 1. Demographics and Clinical Data of All Patients ($n = 72$)

	Mean ± SD	Range
Age (years)	36.15 ± 7.39	20–50
Age of onset (years)	23.44 ± 4.85	13–351
Duration of illness (years)	12.72 ± 6.79	0.5–29[a]
Height (cm)	174.43 ± 7.28	158–191
LP weight haloperidol (kg)	82.77 ± 17.15	56.3–134
LP weight drug free (kg)	83.46 ± 17.11	57.8–136.4
Dose haloperidol (mg/day)	11.28 ± 7.24	2–40[b]
Days drug free prior to LP	38.61 ± 12.65	14–67

[a] DSM-III-R criteria require that symptoms be present for at least 6 months.

[b] One patient received 40 mg haloperidol PO QD.

cated and returned to outpatient treatment. After the protocol was completed and the patients restabilized, the staff discussed with each patient the medication and the behavioral changes throughout his participation.

Normal Control Subjects

Twenty-four carefully screened and age-matched male control subjects (age 35 ± 10 years) were recruited from the community. They were free of psychiatric [SADS-L (Spitzer and Endicott 1979)] or medical illnesses (present or past) and without family history of psychiatric illness. Subjects also passed a urine drug screen. They received an LP after an overnight stay in the hospital under the same standard conditions as the patients. They signed IRB-approved informed consent forms explaining the purpose and risks of research participation and their right to withdraw.

Lumbar Puncture

The LP was performed between 7:30 and 8:30 A.M. after overnight bed rest (van Kammen and Sternberg 1980) with the subject fasting and without smoking from 11:00 P.M. the previous evening until the completion of the procedure, with the patient in the lateral decubitus position. CSF was collected in three pools of 12 ml each in ice-chilled tubes. Each of these pools was thoroughly mixed and subsequently aliquotted in 0.5- and 1-ml tubes and stored at −80°C until assayed. CSF from the first pool was used for HVA measurements.

Blood Draws

Blood draws for plasma HVA were performed at 8:00 A.M., with the subject remaining at bed rest, fasting, and nonsmoking from 11:00 P.M. the previous evening until the completion of the procedure. An 18-gauge IV intracatheter or a 19-gauge butterfly needle was inserted 30 minutes before the first blood draw was obtained. An IV of 500 cc normal saline solution was run at a Keep Vein Open rate between blood draws. The technician then processed the whole blood and pipetted the plasma into nunc tubes containing 1 to 2 ml. The tubes were then immediately stored in a −80°C freezer.

Urine Collection

Twenty-four-hour urine specimens were collected in the 3 days leading up to the LPs in the last 34 of the 72 patients. If collections were less than 900 ml or creatinine levels indicated an inadequate collection, the urine was discarded and an additional 24-hour urine was obtained. Urine was placed in containers with concentrated HCl and refrigerated at 4°C immediately after voiding. Aliquots of the 24-hour urine collections were stored at −20°C until assayed. Creatinine levels in plasma and urine were obtained.

Assays

HVA was determined in CSF, plasma, and urine with high-pressure liquid chromatography (HPLC) utilizing the modified procedures of Scheinin et al. (1983), Gerhardt et al. (1986), and Binder and Sivorinovsky (1984), respectively. Intraassay coefficients of variation were 3.32% at a concentration of 26.75 ng/ml for CSF, 6.59% at a concentration of 27.81 ng/ml for plasma, and 7.5% at a concentration of 1.77 μg/ml for urine. Interassay coefficients of variation were 4.41% at a concentration of 26.75 ng/ml for CSF, 6.96% at a concentration of 27.81 ng/ml for plasma, and 11.12% at a concentration of 1.77 μg/ml for urine. CSF, plasma, and urinary HVA measures did not correlate with storage time in days.

Clearance

Urine volume, plasma creatinine, and creatinine concentration were obtained as concurrent measures of kidney function in order to control for possible effects on HVA clearance. HVA and creatinine clearance were calculated according to the following formula (Maas et al. 1993a), $cl = VC/P$ where cl is creatinine clearance, V = urinary volume, C = urinary concentration, excretion is VC, and P is plasma concentration.

Statistical Analysis

Analysis of variance (ANOVA) was performed to assess relapse, medication, and interaction effects of CSF, plasma, and urinary HVA levels, urinary output of HVA and creatinine, urine volume, and HVA and creatinine clearance. Pearson correlation coefficients were used to determine relationships between demographics, psychosis, and HVA. Student t-tests (paired when appropriate) were used to analyze differences between groups. All tests were two-tailed. Initial inspection of the distributions of HVA variables indicated that plasma HVA had a slightly skewed distribution, thus the values were log-transformed for the purpose of analysis.

RESULTS

Demographics

CSF HVA correlated significantly with age on ($r = -0.25$, $p = .033$) and off haloperidol ($r = -0.31$, $p = .008$), but plasma HVA and the urinary measures did not. None of the drug-free HVA measures were significantly correlated with the time drug free before procedures.

Medication and Clinical Change Effects

Mean CSF HVA values for all 72 subjects were significantly lower after haloperidol withdrawal than before (30.95 ± 15.18 ng/ml versus 27.17 ± 12.13 ng/ml; F = 6.94, df = (1,70), p = .01), indicating a significant medication effect without a relapse or interaction effect (Table 2).

Analysis of plasma HVA values did reveal a marginally significant interaction effect (F = 2.92, df = (1,70), p = .092), showing that patients who had an increase in symptoms following haloperidol withdrawal had increases in plasma HVA, whereas those who remained clinically stable had no significant change in plasma levels (Table 2).

Mean urine volume decreased significantly after haloperidol withdrawal (3.10 ± 1.40 versus 2.42 ± 1.35 L/day; F = 5.23, df = (1,32), p = .03), but mean urinary HVA concentration did not (1.47 ± 1.05 versus 1.41 ± 0.95 μg/ml; F = 0.14, df = (1,32), p = NS). Mean urinary HVA excretion decreased significantly after haloperidol withdrawal (3.60 ± 2.00 versus 2.66 ± 1.54 mg/day; F = 17.02, df = (1,32), $p < .0005$), suggesting that total body production is reduced. HVA clearance also decreased significantly after haloperidol withdrawal (857.99 ± 670.86 versus 527.47 ± 362.47 L/day; F = 13.09, df ± (1,32), p = .001). However, because of a large variance difference between clinical status groups, the ANOVA effects on clearance are tentative.

Urinary creatinine concentration increased significantly following haloperidol withdrawal (607.55 ± 246.07 versus 829.91 ± 430.46 μg/ml; F = 7.16, df = (1,28), p = .012), while the urine volume decreased (see before). Therefore, no significant change in total creatinine output was observed after drug withdrawal (1632.45 ± 408.06 versus 1554.56 ± 473.47 mg/day; F = 0.15, df = (1,28), p = NS). Urinary creatinine clearance did not change significantly following haloperidol withdrawal (164.00 ± 50.01 versus 160.61 ± 45.87 L/day; F = 0.06, df = (1,26), p = NS). These measures provided evidence that kidney function was not impaired in our patients.

Comparison with Controls

CSF HVA was not significantly different between drug-free patients and normal comparison subjects. The relationships among the different compartments with alternating clinical state and medication status are shown in Table 3.

Relationships with Psychosis

Only drug-free CSF HVA values showed a significant (negative) correlation with global psychosis (Bunney and Hamburg 1963) at the time of procedures.

DISCUSSION

Our data indicate that haloperidol withdrawal markedly decreased HVA function and excretion in schizo-

Table 2. CSF and Plasma in Normal Control Subjects and in Schizophrenic Patients during Haloperidol Treatment and after Haloperidol Withdrawal

	Haloperidol (mean ± SD)	Drug Free (mean ± SD)	*n*
CSF HVA (ng/ml)			
Normal subjects	NA	28.41 ± 12.01	24
Nonrelapsers	31.76 ± 16.67	29.32 ± 1328	40
Relapsers	29.93 ± 13.27	24.49 ± 10.10	32
Plasma HVA (ng/ml)[a]			
Nonrelapsers	6.81 ± 3.91	6.31 ± 2.52	40
Relapsers	5.43 ± 2.66	6.68 ± 3.52	32
Urinary HVA-total (mg/day)			
Nonrelapsers	4.02 ± 2.22	3.09 ± 1.75	13
Relapsers	3.34 ± 1.86	2.40 ± 1.37	21
Urinary HVA-conc. (μg/ml)			
Nonrelapsers	1.72 ± 1.10	1.71 ± 1.12	13
Relapsers	1.31 ± 1.01	1.22 ± 0.80	21
Urinary HVA-clearance (L/day)			
Nonrelapsers	963.27 ± 912.57	564.34 ± 408.33	13
Relapsers	792.81 ± 480.89	504.64 ± 339.58	21

Abbreviations: HVA = homovanillic acid, urinary HVA-total = total urinary HVA in mg/day (mean of 3-day collection, urinary HVA-conc. = urinary HVA concentration in mg/L, urinary HVA clearance = (volume × HVA-conc.)/plasma concentration, CSF HVA = cerebrospinal fluid HVA.

No relapse effects or relapse × medication effects were observed.

[a] Values log transformed for analysis.

Table 3. Relationships between HVA Measures in the Different Compartments, on and off Haloperidol

	Plasma HVA	Urinary HVA-conc.	Urinary HVA-total
Haloperidol			
Relapsers			
CSF HVA	0.24	−0.32	−0.05
Plasma HVA		−0.07	−0.00
Urinary HVA-conc.			0.84[a]
Nonrelapsers			
CSF HVA	0.08	0.01	−0.05
Plasma HVA		−0.16	−0.21
Urinary HVA-conc.			0.93[a]
Drug free			
Relapsers			
CSF HVA	0.37[a]	−0.44[a]	−0.44[a]
Plasma HVA		−0.04	−0.13
Urinary HVA-conc.			0.76[a]
Nonrelapsers			
CSF HVA	0.15	0.06	−0.06
Plasma HVA		0.23	0.20
Urinary HVA-conc.			0.73[a]

Abbreviations: HVA = homovanillic acid, CSF HVA = cerebrospinal fluid HVA, urinary HVA-conc. = urinary HVA concentration in mg/L, urinary HVA-total = total urinary HVA in mg/day (mean of 3-day collection).

[a] $p < .05$.

phrenic patients. Change in psychosis (i.e., relapse status), however, had a very limited effect. CSF HVA and renal HVA excretion declined with drug withdrawal regardless of clinical change. Plasma HVA increased significantly which could be due to the increased transfer out of the CSF and decreased renal clearance. Plasma HVA increased mainly in those who met relapse criteria. We found that CSF HVA decreased slightly more and plasma HVA increased significantly in those who met relapse criteria compared to those who remained clinically stable following drug withdrawal (Figure 1). Patients who showed a symptom exacerbation and those who remained clinically stable were not different in age, age of onset, duration of illness, or premorbid functioning (data not shown). Psychosis correlated negatively with CSF HVA but not significantly with plasma HVA. The correlations between HVA in the different compartments were stronger in the relapsers (on and off haloperidol) and particularly in the drug-free relapsers. This suggests that during relapse, brain HVA contributes more to HVA in plasma and urine, whereas during clinical stability central dopamine turnover is not related to plasma or urinary HVA.

How Do CSF, Plasma, and Urinary HVA Relate to Brain Dopamine Turnover?

To interpret the observed changes in steady-state HVA after drug withdrawal and relapse, we need to take into account the origins and metabolism of HVA as well as the adaptive changes in the dopaminergic system caused by chronic haloperidol administration. Because plasma HVA does not enter the CSF (Elchisak et al. 1978), CSF HVA is believed to be exclusively of central origin. However, studies in rats suggest that only approximately 3.5% of brain HVA ends up in the CSF (Aizenstein and Korf 1978). In primates the percentage of brain HVA going to the CSF may be larger because of a larger cortical dopamine pool than in rodents (Stanley et al. 1985; Elsworth et al. 1987).

Most of the brain HVA enters directly into the blood supplying some of the plasma HVA (Kopin et al. 1988b; Lambert et al. 1993; Maas et al. 1993b). The rest of plasma HVA may be derived from peripheral noradrenergic neurons (Hoedtke et al. 1974; Kopin et al. 1988b; Maas et al. 1993b). Plasma HVA has long been believed to be a measure of central dopaminergic activity in humans (Cutler et al. 1982; Sternberg et al. 1983; Sharma et al. 1989). Some changes in plasma HVA reflect changes in activity in the presumed central regions of origin: the subcortical structures, in particular the basal ganglia (Lambert et al. 1993).

Twenty-five percent of urinary HVA originates in the central nervous system (Maas et al. 1979; Kopin et al. 1988a), with the remaining 75% coming from dopamine derived from peripheral noradrenergic neurons metabolized in the liver (Andèn and Grabowska-Andèn 1983; Maas et al. 1993b; Lambert et al. 1994). Loss of dopa-

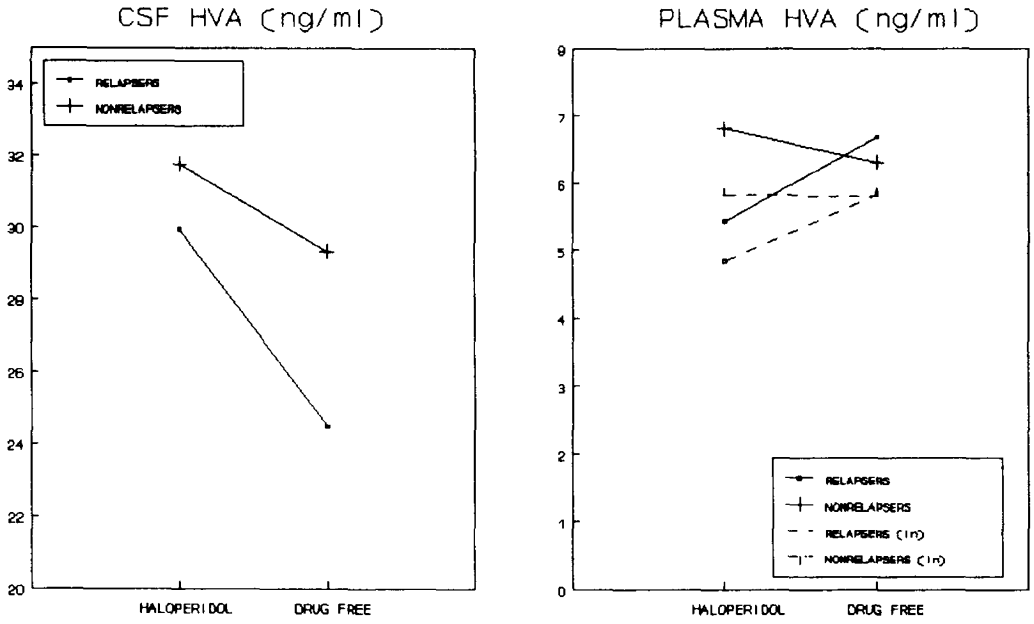

Figure 1. Haloperidol withdrawal: repeated-measures ANOVA CSF and Plasma HVA. Relapsers were patients who met specific criteria for symptom increase, nonrelapsers were patients who remained clinically stable. ln, natural log; plasma data were transformed for analysis and then the means were exponentiated to reconstruct the comparisons.

mine (DA) neurons results in a decrease in urinary HVA (Hoedtke et al. 1974). Plasma HVA is almost exclusively cleared by the kidneys (Miller et al. 1987) through glomerular filtration and active tubular secretion by means of an active organic anion transport system. Most likely HVA is reabsorbed in the distal tubules (Ånggard et al. 1974), because clearance decreased with a decrease in urinary flow. HVA competes with other organic anions such as 5-HIAA, and urinary pH affects HVA clearance (Amin et al. 1992). The antipsychotic drug effects on total urine volume (Crowley et al. 1978), HVA output (Karoum et al. 1987), HVA renal clearance (Maas et al. 1993b), and the lack of a drug effect on urinary HVA concentration have been reported before, but not the evaluation of a clinical state change effect. In the nonrelapsers the changes in plasma HVA (i.e., from the brain) may have been offset by the decreased renal clearance, but the increased brain and decreased renal clearance in the relapsers led to an increase in plasma HVA.

Traditionally, the proposed major source of CSF HVA has been the striatum, which lies in close proximity to the lateral ventricles, in addition to the putamen and the nucleus accumbens (Bacopoulos et al. 1978) based on studies in rodents (Sourkes 1973; Amin et al. 1992). However, no significant relationship was found between CSF HVA and HVA in the basal ganglia of nonhuman primates by Elsworth et al. (1987). They did find a significant correlation between cisternal CSF HVA and HVA in the dorsofrontal cortex, which may be explained by the much larger cortical production of HVA in primates than in rodents. A similar correlation between HVA in CSF and the frontal cortex was found in human autopsy studies (Stanley et al. 1985). In schizophrenic patients cortical atrophy (van Kammen et al. 1986), decreased frontal blood flow (Weinberger et al. 1988), and increased ventricle brain ratios (VBR) (van Kammen et al. 1983, 1986; Nybäck et al. 1983; Jennings et al. 1985; Houston et al. 1986; Losonczy et al. 1986; Doran et al. 1987; Lewine et al. 1991) have been associated with lower CSF HVA. In normals CSF HVA levels did not correlate significantly with VBR, nor were CSF HVA levels different from those in patients (Nybäck et al. 1983). This suggests that much of the human CSF HVA in schizophrenic patients is of frontal cortical origin.

Haloperidol Withdrawal

Haloperidol withdrawal had a significant influence on HVA levels and on urinary HVA excretion. The decrease in CSF HVA following drug withdrawal has been noted before, without defining which patients had changed clinically (Bartkó et al. 1987; Pickar et al. 1990), while a lack of changes were observed if no relapsed patients were included (Zander et al. 1981; Bagdy et al. 1985; Frecska et al. 1985). A dopamine receptor rebound following drug withdrawal in schizophrenic patients has been hypothesized but not confirmed (van Kammen et al. 1982a), which could explain the decrease in brain HVA output (Bagdy et al. 1985; Frecska et al. 1985). Recent data suggest that D_4 receptor supersensitivity could be present in schizophrenia (Seeman 1992), although it is unclear as yet how much this affects total dopamine turnover. In addition, an increase in CSF

clearance of HVA compared to the on-haloperidol condition might also partially explain the decrease in CSF HVA. HVA is transported across the brain-blood barrier by a probenecid sensitive organic anion transport system (Moleman et al. 1978; Westerink and Kikkert 1986) that is inhibited by haloperidol.

Clinical stability at 6 weeks drug free was associated with a nonsignificant decrease in CSF and plasma HVA, which may reflect a modest drug effect on dopamine turnover. For those who relapsed a more complex pattern emerged: CSF HVA decreased and plasma HVA levels increased significantly. Because urinary HVA clearance and production declined similarly in both patient groups (Figure 2), the differences observed in CSF and plasma HVA between these groups may reflect decreased cortical or increased hippocampal input on other dopamine projection areas. It is conceivable that increased dopamine activity in subcortical areas and the temporal lobe suppressed cortical dopamine turnover (Pycock et al. 1980; Scatton et al. 1982; Haroutunian et al. 1988).

Our data provide only weak evidence that relapse may be associated with a relatively greater decrease in CSF HVA following drug withdrawal. It confirms the repeated inability to find a significant increase in CSF HVA in schizophrenic patients as evidence of dopamine overactivity. In contrast, the present-day understanding of the intrabrain dopamine dynamics suggests an early temporal lobe lesion-associated decrease in dopamine turnover in the prefrontal cortex and increased mesolimbic and striatal dopamine release (Lipska et al. 1994, in press a). That only trend level significance was reached may be explained by an increase in variance due to the concentration gradient of HVA down the spinal cord (Sourkes 1973; Garelis et al. 1974). The potentially larger decrease in CSF HVA in relapsed patients may be explained by greater D_2 (or D_4) receptor sensitivity leading to a greater decrease in dopamine release or a greater ventral hippocampal activity in relapsed patients [Csernansky et al. 1988a]. For this hypothesis to be tested SPECT or PET measurements of dopamine receptor activity in relapsed patients may need to be obtained. So far, such data have not been forthcoming.

Several groups have reported that increases in symptoms within 3 to 6 weeks following drug withdrawal were associated with increases in plasma HVA (Pickar et al. 1986; Glazer et al. 1989; Davidson et al. 1991). In addition, plasma HVA may also differ between clinical states, if the mesolimbic brain activates the peripheral autonomic nervous system with relapse (Dawson et al. 1994) [i.e., increased peripheral dopamine converted into HVA (Andèn and Grobowska-Andèn 1983; Maas et al. 1993b; Lambert et al. 1994)]. However, peripheral autonomic arousal does not equate with psychosis but may be a mixed trait and state marker (Dawson et al. 1994; Zahn 1988).

The attenuated frontal cortical dopamine release (CSF HVA) in patients with structural or functional cortical changes (Nybåck et al. 1983; Stanley et al. 1985; van Kammen et al. 1983, 1986; Doran et al. 1983; Weinberger et al. 1988) and the relative increase in plasma HVA in relapsers may reflect decreased cortical and increased mesolimbic and temporal lobe dopamine release or activity (Sourkes 1973; Weinberger 1987; Csernansky et al.

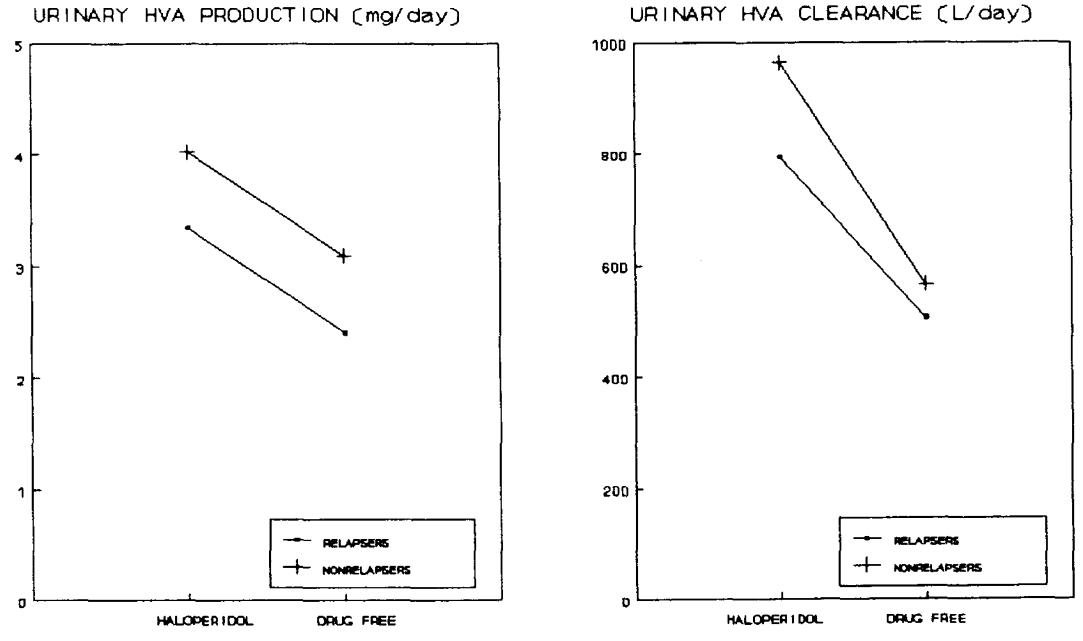

Figure 2. Haloperidol withdrawal: repeated-measures ANOVA urinary HVA production and clearance. Urinary HVA production (mg/day; mean of 3-day collection. HVA clearance (L/day), (volume × HVA-concentration)/plasma concentration.

1988b; Gur et al. 1995). The recent studies of Lipska et al. (1992, 1993, 1994, in press b) raise an interesting possibility that neonatal lesions or temporal lobe alterations may decrease cortical and increase subcortical HVA production.

van Kammen and coworkers (van Kammen and van Kammen 1984; van Kammen et al. 1996) have proposed that the monoamine changes in relapse-prone schizophrenic patients reflect increased stress sensitivity (Antelman et al. 1988), which can be muted by antipsychotic drug treatment (van Kammen 1991) Breier et al. (1993) reported that schizophrenic patients, as compared to normal volunteers, had significantly greater 2-deoxyglucose-induced plasma HVA increases. These plasma HVA peak changes correlated inversely with frontal cortex volume as measured with magnetic resonance imaging in the schizophrenic patients. The abnormal dopamine response to stress may be mediated through reduced cortical inhibitory influences. Plasma cortisol increases were similar in the two groups, raising the possibility that the plasma HVA response to stress is specific for schizophrenia (Breier et al. 1993). Whether our results indeed point to a greater stress sensitivity as indicated by relatively decreased CSF HVA and increased plasma HVA levels leading to an increase in psychosis or that the stress of the psychosis increase leads to these changes in dopamine release remains to be determined. The questions of how and why dopamine and schizophrenia are linked may need to be addressed in concurrent on- and off-drug evaluations of the serotonin (Meltzer 1991), the noradrenergic system (Hornykiewicz 1982, Grenhoff et al. 1993), the glutamate (Zukin and Javitt 1992), the GABA (van Kammen et al. 1982b, submitted), or the cholinergic systems (Karson et al. 1991; Tandon et al. 1991; Yeomans 1995); which all interact with or influence the dopamine system.

The changes in psychosis can now be understood in terms of changes in intrabrain dynamics or connectivity during clinical states rather than gross changes in dopamine release (Weinberger 1987; Lipska et al. in press b). Indeed, the apparent paradox of decreased CSF HVA (Bowers et al. 1980; Lindström 1985; Pickar et al. 1990)—in the absence of differences with normals—and higher plasma HVA with higher psychosis observed by others (Davis et al. 1985, Borg et al. 1985; Pickar et al. 1986; Davila et al. 1988; Maas et al. 1988; Glazer et al. 1989; Javaid et al. 1990; Muscettola et al. 1990; Baker et al. 1991; Davidson et al. 1991) with decreased urinary clearance becomes then understandable. Our data raise the additional possibility that peripheral regulation of plasma HVA is altered with relapse without clarifying the potential mechanism of this change, because haloperidol withdrawal decreased urinary clearance in all subjects. Conceivably, dopamine involvement in schizophrenia reflects the failure of homeostatic mechanisms in the brain that facilitate the integration of different functional components (van Kammen et al. 1995).

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