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# Monoamine activity reflected in urine of young patients with obsessive compulsive disorder, psychosis with and without reality distortion and healthy subjects: an explorative analysis

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**Summary.** Positive psychotic symptoms are reported to be associated with high, negative symptoms with low dopamine (DA) activity and serotonin (5HT) activity may be altered in obsessive-compulsive disorder (OCD). We analysed 24 h urine samples in these patient groups and in healthy controls for supportive evidence. Young unmedicated OCD subjects excreted more adrenaline (AD) and homovanillic acid (HVA) and showed a higher HVA/MHPG ratio and metabolic rate than healthy controls. Independent of general metabolic rate they showed higher HVA concentrations which suggests that the relative activity of catecholamine systems in OCD (HVA/MHPG) is due more to high DA than to low noradrenergic (NA) activity. Concentrations of 5HT were also high in OCD patients. In psychotic patients low levels of DA, HVA, NA and MHPG probably resulted from neuroleptic medication. Patients diagnosed with paranoid psychosis showed higher DA utilization than controls and those with few paranoid symptoms showed high 5HT utilization. These results support studies suggesting that paranoid psychosis is associated more with increased DA activity (discussed in the context of neuroleptic reactivity), that non-paranoid forms are associated more with increased 5HT activity and that OCD patients are unusually aroused with high levels of Ad, 5HT and HVA.

**Keywords:** Obsessive-compulsive disorder, schizophrenia, paranoia, adrenalin, noradrenalin, dopamine, serotonin, urine.

## Introduction

Neuroleptics and serotonin-uptake blockers are effective in restricting the expression of symptoms, respectively, in schizophrenia (Straube and Oades, 1992) and obsessive compulsive disorder (OCD: Pigott et al., 1990). This has

led to a widespread belief that dopamine (DA) and serotonin (5HT) metabolism may be altered in these two illnesses.

However, the efficacy of 5HT antagonists in some schizophrenics (Bleich et al., 1988) and evidence of unusual DA metabolism in some OCD patients (Marazziti et al., 1992) gives rise to the possibility that the metabolism of *both* monoamines may be altered in *both* illnesses. As the nature of the differences has been difficult to identify, we decided to collect 24 h urine samples of amines and metabolites to investigate the relationship of general neurotransmitter activity in psychotic and OCD patients to performance in a psychological test battery. Here we report the biochemical findings.

Noradrenaline (NA) and its metabolite 3-methoxy-4-hydroxy-phenylglycol (MHPG) were also measured as a control for signs of DA metabolic changes (see below) and as there have been indications of changes of NA metabolism in psychotic (Hornykiewicz, 1982) and OCD patients (Hollander et al., 1991).

This study was performed with adolescent and young adult subjects. The first reason is that while the differential diagnosis between psychosis and OCD is clear cut in adults, in adolescents psychosis not infrequently develops out of early compulsive traits (Eggers, 1968; Thomsen, 1992). The second reason for studying young patients is that we wished to compare the state of their transmitter metabolism during periods of active symptom expression shortly after admission in an early episode of their illness. Here we enhanced this contrast in the psychotic patients by comparing those with and without a diagnosis of paranoid schizophrenia (*P-diag vs NP-diag*) with those with high and low ratings of paranoid delusions and hallucinations (*P-symp vs NP-symp*). This accords with the recent advocation by Potter and Manji (1993) of the study of the relationship between metabolites in body fluids and clusters of symptoms. A potential difference between these subgroups is supported by the finding of different topographic distributions of mismatch negativity and difference negativity in event-related potentials in relation to active symptoms (Oades, 1993; Oades et al., 1993).

What are the advantages and disadvantages of the measurement of neurotransmitters and their metabolites in urine? First and foremost it should be appreciated that amines and their metabolites in urine will have their origin in somatic *and* CNS sources (Moleman et al., 1992; Amin et al., 1992) and thus in psychiatric patients illness-related factors affecting amine activity will be represented *as a part* of the total excretion measured. Secondly, indications of metabolic activity (not referring to production or disappearance rates) must take into account levels of metabolites *and* the parent amine.

Some advantages of urinary measures are as follows. 1) As far as is known most transmitter metabolites, in particular HVA, are removed in urine, (the contribution of bile is uncertain): 2) By collecting for a specified period, metabolites can be expressed per unit time: 3) Collection is non-invasive and painless: 4) 24 h measures are likely to reflect average daily production rates and are less likely to be affected by short term fluctuations (e.g., brief exercise);

the cumulative nature of the 24 h measure means that it will be more sensitive to minor changes of HVA production than single samples of other fluids (Contreras et al., 1988).

Some disadvantages of urinary measures are as follows. 1) Collection requires reliable cooperative subjects, which is not the rule with psychiatric patients: but problems can be minimized by ward staff and the co-operation of the patient can be enhanced through individual arrangements and the development of a relationship with the supervising doctor. 2) As an indicator of central DA activity, urinary HVA measures are compromized by other sources, notably NA neurons (c. 75%). However, *simultaneous monitoring of MHPG* can help determine if HVA changes are likely to reflect changes of NA metabolism and activity (see comprehensive discussion in Amin et al., 1992). Other sources of urinary HVA are peripheral DA and peripheral NA cells, neurons and terminals (Kopin et al., 1988; Maas et al., 1980).

Practical reasons restricted us to measuring one major metabolite of NA. MHPG was chosen as it is the major metabolite reflecting NA transmission in the brain, although it is also formed in peripheral systems (Moleman et al., 1992). Other metabolites derive primarily from peripheral systems or are more indirect indicators of neurotransmission (e.g., metanephrine, normetanephrine and vanillomandelic acid). However, urinary MHPG levels are reported to correlate with those of vanillomandelic acid and to covary with plasma and tissue levels (Kopin, 1985) which in turn correspond to those in the brain (Lechman and Maas, 1984). It has been claimed that 20–30% of urinary MHPG derives from the CNS (Maas et al., 1980; Kopin et al., 1984) and diagnostically useful D-type scores are reported to correlate best with MHPG (Schatzberg et al., 1989).

We report urinary levels of monoamines (Ad, DA, NA, 5HT) and the metabolites (HVA, MHPG, 5HIAA) under the following explicit assumptions: 1) it is likely that over an extended period excretion rates equal formation rates (Anggard et al., 1975; Elchisak et al., 1982); 2) Under physiological conditions monoamine and metabolite formation depends mainly on impulse flow and secondarily on availability and concentration of presynaptic sites, amino acids and cofactors (Amin et al., 1992).

## Methods

### *Subjects*

From an original group of 33 psychotic patients (including 2 outpatients) data from 27 are reported. Data from 6 are not reported as two did not satisfy DSM IIIR and ICD 9 criteria for schizophrenia or schizoaffective disorder and 4 provided inadequate urine samples. Three of the patients were unmedicated: the dominant neuroleptic medication in the others was clozapine (n = 5), butyrophenone or fluphenazine (n = 18) and one subject received predominantly perazine (see Table 1). Two patients received beta-blockers and were excluded from evaluations of data based on NA.

Patients were diagnosed to the following subgroups - 12 paranoid (295.3), 6 disorganized (295.1), 7 schizoaffective (295.7), 1 schizophreniform (295.4) and 1 undifferentiated (295.9). With respect to the schizoaffective patients we note Werry's warning (1992) that this group

**Table 1.** Group comparisons for age, gender, medication and urine collection (mean and sd)

| | Age (y) | Gender | | Urine volume (ml) | Creatinine (mg/d) | Medication (CPZ equivs) |
|---|---|---|---|---|---|---|
| | | m | f | | | |
| Psychosis | 18.4 | 14 | 13 | **1748**[1] | 1314 | 959 |
| n = 27 | 3.5 | | | 918 | 540 | 1104 |
| P-diag | 18.1 | 7 | 5 | 1684 | 1343 | 1425 |
| n = 12 | 3.1 | | | 650 | 473 | 1378 |
| NP-diag | 18.6 | 7 | 8 | 1799 | 1290 | 587 |
| n = 15 | 3.8 | | | 1107 | 604 | 661 |
| P-symp | 18.7 | 9 | 5 | 1746 | 1298 | 932 |
| n = 14 | 3.5 | | | 726 | 441 | 822 |
| NP-symp | 18.0 | 5 | 8 | 1749 | 1332 | 989 |
| n = 13 | 3.5 | | | 1120 | 648 | 1380 |
| OCD | 16.4 | 8 | 3 | 972 | 1266 | none |
| n = 11 | 2.8 | | | 720 | 705 | |
| Controls | 18.1 | 13 | 14 | 985 | 1426 | none |
| n = 27 | 3.6 | | | 339 | 455 | |

1. $p < 0.02$ (psychotics vs OCD and controls)

is difficult to differentiate from bipolar psychosis in young or adolescent patients. Two of our patients for whom the diagnosis 295.70 was agreed did show some bipolar features. For a third patient a diagnosis of reactive psychosis was rejected on the formal criterion of duration.

Psychotic patients were subdivided into those with a diagnosis of paranoid schizophrenia (295.3) and those with other subtypes of nonparanoid psychosis (295. × ). These subgroups are called *P-diag* and *NP-diag* (Table 1). They all received a semi-structured interview for the assessment of positive and negative symptoms (Andreasen, 1983, 1984) which was rated by a clinician, two clinical psychologists and a psychobiologist (Spearman rho for all 64 questions ranged from 0.64–0.75 between subjects). A median split (score of 7) on the scores for delusions and hallucinations separated the paranoid-symptom group (*P-symp*) from the nonparanoid symptom group (*NP-symp*). The period covered by the questions at interview was that in which the urine was collected.

From 13 unmedicated OCD inpatients studied (300.3, DSM IIIR) two provided inadequate urine samples and the data were excluded. There was no comorbidity with other diagnosis except for one case of trichotillomania.

From 56 healthy subjects (aged 8–26 y) studied we paired 27 with the psychotic patients matching for gender and for age within 4 months. These subjects reported no psychiatric complaints or major medical problems and were free of medication at the time of testing (Table 1).

### *Collection methods*

Urine was collected over 24 h in 21 bottles over 50 ml hydrochloric acid. Samples excluded the first morning toilet visit and continued until the next day when the first sample was

included. All subjects were asked not to eat foods with high amine content or that affect amine activity (e.g., refrain from chocolate, nuts, bananas, tomatoes, citrus fruit and drinks containing caffeine). Overnight fasting of ca. 14 h eliminates the effect of diet on plasma HVA (Davidson et al., 1987). It was not possible to control for smoking.

Conventional expectations that a litre of urine should contain 800 mg creatinine were fulfilled for adults. Values 33% lower were accepted for small 12–14 y olds. It should be pointed out that except in the cases rejected (see above) psychotics generally produced more urine than controls ($t - 2.5$ & $- 4.1$, $p < 0.02$) but all groups produced equivalent amounts of creatinine over 24 h (Table 1). Further it was made explicit to the controls that payment of the DM 50 honorarium for participation in the test battery was contingent on a responsible full urine collection.

Collections were shaken and eight 10 ml monovette samples were taken on the same morning and deep frozen ($- 25\,^{\circ}C$) until analysis. The catecholamines adrenaline (AD), noradrenaline (NA) and dopamine (DA) were assayed blind to subject group by ion exchange chromatography with fluorescence detection (Werner, 1975). These results were checked in a second laboratory (Boos and Wilmers, 1988). Intra- and inter-assay variations ranged from 3–6% and 4–8%, respectively. Serotonin (5-HT) analysis followed the instruction manual of Chromsystems (Oct 1990, Munich). Intra-assay variation was under 3%. Analysis of the monoamine metabolites homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MFPG) and 5-hydroxy-indoleacetic acid (5-HIAA) was performed by liquid chromatography and fluorescence detection (Gironi et al., 1988). Based on a sample of ten, the intra- and inter-assay variations ranged from 2–6% and 4–7%, respectively.

It should be emphasized that the data presented should not be taken as absolute values. Repeated measures in the same laboratory may show relatively low variance (see above) and may correlate with measures elsewhere while varying by 20% in absolute terms (Potter and Linnoila, 1989). But where absolute values are low, the variance between laboratories can be high (e.g., AD, Schatzberg et al., 1989, p 266). If we consider adrenergic measures varying by 2 standard deviations from the mean we recorded one such value for AD and NA from a schizophrenic and one NA value for an OCD patient.

### *Data and analysis*

Amine and metabolite measures were corrected for volume and calculated as excretion rates per litre and per 24 h. These values were expressed per nanogram creatinine to correct for general somatic metabolic rates and per square metre body area to further control for the variations implicit in a study including children ($< 1\,m^2$) and young adults ($> 2.2\,m^2$: Oades et al., 1990).

Multivariate analysis of urinary data (see text) was followed by univariate and conservative post-hoc Scheffe tests (with a conservative 5% alpha; see Tables). Tests for homogeneity varied between measures (e.g., all HVA measures were homogenous; 5-HIAA measures were not homogeneous for psychotic and control subjects). Therefore parametric tests were followed by Mann-Whitney (M-W) comparisons (see table legends; Bornstein and Baker, 1992). Student t-tests were used for measures derived from more than one transmitter as the values compared were not entirely independent of each other. Pearson correlation coefficients are also reported.

## Results

### *Monoamines and metabolites*

Analysis of the 7 monoamines and metabolites showed that OCD subjects excreted significantly more AD and HVA than healthy controls. Other measures

were not significant ($F(14, 112) = 2.1$, $p < 0.02$; Scheffe, AD $p = 0.003$, HVA $p < 0.03$). The OCD measures tended to be higher than in the psychotic group (AD, HVA $p < 0.09$: Table 2).

The essential difference for the OCD group remained when the psychotic group was subdivided; i.e., compared with P-diag/NP-diag ($F(21, 168) = 1.7$, $p < 0.04$) or with P-symp/NP-symp ($F(21, 168) = 2.1$, $p < 0.01$; Scheffe AD $p < 0.01$, HVA $p = 0.05$).

Covarying for medication (CPZ equivalents) and age made no substantive difference: significance marginally decreased in the diagnostic comparison and marginally increased in the active symptom comparison (AD for OCD vs controls $p < 0.003$, vs P-symp $p < 0.08$, vs NP-symp $p < 0.09$: HVA for OCD vs controls $p < 0.05$, vs psychotic groups $0.4 < p < 0.2$). There were no significant

**Table 2.** Monoamines and their metabolites by group (ng/mg creatine/$m^2$) (mean and sd)

| Subjects | Substance | | | | | | |
|---|---|---|---|---|---|---|---|
| | AD | DA | HVA | NA | MHPG | 5HT | 5HIAA |
| Psychosis | 3.7 | 284 | 1872 | 15 | 936 | 60 | 1416 |
| (n = 27) | 3.0 | 369 | 899 | 10 | 1050 | 72 | 1514 |
| P-diag | 2.9 | 182 | 2112 | 16 | 906 | 69 | 1483 |
| (n = 12) | 2.4 | 157 | 1039 | 12 | 712 | 82 | 1433 |
| NP-diag | 4.3 | 367 | 1680 | 13 | 780 | 54 | 1362 |
| (n = 15) | 3.3 | 466 | 751 | 8 | 1166 | 67 | 1623 |
| P-symp | 4.3 | 224 | 1982 | 14 | 923 | 58 | 1402 |
| (n = 14) | 3.5 | 320 | 1103 | 6 | 702 | 66 | 1333 |
| NP-symp | 3.3 | 349 | 1754 | 15 | 764 | 63 | 1431 |
| (n = 13) | 2.3 | 418 | 636 | 13 | 1169 | 82 | 1744 |
| OCD | **5.8**[1] | 372 | **2623**[2] | 21 | 689 | **97**[4] | **1371**[3] |
| (n = 11) | 3.9 | 486 | 1561 | 15 | 652 | 68 | 1228 |
| Controls | 2.4 | 228 | 1651 | 15 | 689 | 57 | 833 |
| (n = 27) | 1.4 | 142 | 626 | 5 | 460 | 75 | 1305 |

1. AD **$p < 0.01$** Scheffe, $U = 67$, $z - 2.6$, **$p < 0.01$** M-W OCD vs controls;
   AD $p < 0.09$ Scheffe, $U = 82$, $z - 1.9$, **$p = 0.05$** M-W OCD vs psychotics;
   $U = 39$–$42$, $z - 1.6/-1.7$ $p = 0.09$–$0.10$ M-W OCD vs P/NP-symp;
   $U = 35$–$46$, $z - 1.9/-1.5$ $p = 0.06$–$0.15$ M-W OCD vs P/NP-diag;
2. HVA **$p < 0.05$** Scheffe, $U = 81$, $z - 2.2$, **$p < 0.03$** M-W OCD vs controls;
   HVA $p < 0.09$ Scheffe, $U = 105$, $z - 1.1$, $p = 0.26$ M-W OCD vs psychotics;
3. 5HIAA $p < 0.57$ Scheffe, $U = 86$, $z - 2.0$, **$p < 0.04$** M-W OCD vs controls;
4. 5HT $p < 0.33$ Scheffe, $U = 91$, $z - 1.9$, **$p < 0.04$** M-W OCD vs controls;
   5HT $p < 0.43$ Scheffe, $U = 83$, $z - 1.7$, $p < 0.08$ M-W OCD vs psychotics;
   $U = 35$–$48$, $z - 1.7/-1.4$ $p = 0.09$–$0.17$ M-W OCD vs P/NP-symp;
   $U = 41$–$42$, $z - 1.3/-1.7$ $p = 0.09$–$0.20$ M-W OCD vs P/NP-diag

correlations between medication and DA ($r = -0.08$) or HVA ($r = +0.17$) for psychotic patients. (For relationships between measures and age see below).

Data on 5 HT for psychotic and 5 HIAA for controls were not homogeneous. 5 HT levels for OCD subjects were clearly higher than in controls and tended to be higher than in the psychotic group. OCD 5 HIAA-levels were higher than in the controls but equivalent to those in psychotic patients (see non-parametric analysis Table 2).

### *Monoamine utilization*

Monoamine activity is reflected by the measure of utilization (level of the metabolite divided by that of the parent amine). For the three subject groups a significant analysis of variance resulted from higher 5 HT utilization in those with psychosis with respect to controls ($F(6, 112) = 3.0$, $p < 0.01$, Scheffe, $p < 0.008$) and to a lesser extent with respect to OCD (Scheffe, $p < 0.08$). Higher levels of NA and DA utilization in the psychotic group, as a whole, were not significant (Table 3).

A significant analysis of variance for the three utilization measures in the 4 subgroups (P/NP-symp; $F(9, 180) = 2.2$, $p < 0.03$: P/NP-diag; $F = 2.8$, $p < 0.005$ was largely attributable to increased 5 HT metabolism in the non-paranoid groups with respect to healthy subjects (Scheffe $p < 0.04$). While 5 HT utilization was nearly as high in the paranoid group this was not significant. 5 HT utilization in the OCDs was similar to that of the controls.

Significance in the analysis by diagnosis was also attributable to increased DA utilization in the P-diag group (Scheffe $p < 0.02$). Only a trend for increased DA utilization was evident in P-symp group (Scheffe, $p < 0.08$). The P-diag and P-symp groups showed a trend to higher DA utilization than the NP-diag and NP-symp groups ($p < 0.07$ and $p < 0.09$, respectively). Age and medication as covariates marginally increased and decreased significance for P/NP-symp and P/NP-diag groups ($F(9, 168) = 2.7$, 2.6, respectively). Significant results were confirmed in the non-parametric analysis.

The non-parametric analysis showed for the psychotic group whether or not it was subdivided into the P- or NP-groups, that NA utilization was higher than in the OCD or healthy groups (Table 3).

### *Relative monoamine activity*

In view of the above differences we compared the following relative measures between groups: DA/NA, HVA/MHPG and HVA/HIAA. There was an unusually high HVA/MHPG ratio in the OCD group compared to controls ($p < 0.013$, Table 4). The NP-symp group also showed a higher HVA/MHPG ratio than controls ($p < 0.03$). No other comparisons approached significance. The apparently low HVA/5 HIAA ratio in the OCD group was not significant as the variation in the other groups was large.

**Table 3.** Utilization of three monoamines by group (means)

| Subjects | Utilization | | |
|---|---|---|---|
| | Dopamine HVA/DA | Noradrenaline MHPG/NA | Serotonin 5HIAA/5HT |
| Psychosis | 12.7 | **79.4**[7] | **33.1**[3] |
| (sd) | 9.5 | 98.2 | 23.3 |
| P-diag | **16.4**[1] | **78.5**[6] | 31.0 |
| (sd) | 10.3 | 58.5 | 20.2 |
| NP-diag | 9.7 | 80.2 | 34.7 |
| (sd) | 7.9 | 127.0 | 25.9 |
| P-symp | **14.8**[2] | **75.2**[5] | 30.2 |
| (sd) | 10.7 | 59.1 | 18.7 |
| NP-symp | 10.4 | 83.2 | **36.0**[4] |
| (sd) | 7.9 | 126.7 | 27.5 |
| OCD | 10.6 | 35.0 | 18.2 |
| (sd) | 4.0 | 20.2 | 11.0 |
| Controls | 9.1 | 43.9 | 17.2 |
| (sd) | 4.4 | 21.1 | 15.1 |

1. DA util
   **p < 0.02** Scheffe, U = 85, z − 2.34 **p < 0.02** M-W P-diag vs controls;
2. p < 0.08 Scheffe, U = 103, z − 1.80 p < 0.07 M-W P-symp vs controls;
   U = 53, z − 1.36 p < 0.17 M-W P-symp vs NP-symp;
   U = 67, z − 1.63 p < 0.10 M-W P-diag vs NP-diag;
3. 5HT util
   **p < 0.01** Scheffe, U = 166, z − 2.97 **p < 0.01** M-W psychotics vs controls;
   p < 0.07 Scheffe, U = 78, z − 1.92 p < 0.06 M-W psychotics vs OCD;
4. p < 0.22 Scheffe, U = 79, z − 2.22 **p < 0.03** M-W P-symp vs controls;
   **p < 0.03** Scheffe, U = 87, z − 2.56 **p < 0.01** M-W NP-symp vs controls;
   p < 0.23 Scheffe, U = 80, z − 2.19 **p < 0.03** M-W P-diag vs controls;
   **p < 0.04** Scheffe, U = 86, z − 2.58 **p < 0.01** M-W NP-diag vs controls;
5. NA util
   p < 0.7 Scheffe, U = 33, z − 2.0, **p < 0.04** M-W P-symp vs OCD;
   p < 0.8 Scheffe, U = 101, z − 1.9, p < 0.06 M-W P-symp vs controls;
6. p < 0.4 Scheffe, U = 27, z − 2.4, **p < 0.02** M-W P-diag vs OCD;
   p < 0.5 Scheffe, U = 86, z − 2.3, **p < 0.02** M-W P-diag vs controls;
7. p < 0.13 Scheffe, U = 88, z − 1.7, p < 0.09 M-W psychotics vs controls

### *Concentration measures*

Creatinine concentrations indicated a high metabolic rate in the OCD patients (means for psychotics 890, OCD 1741 and controls 1559 mg/l). The low value for psychotic subjects was attributable to their producing more urine. It is therefore not surprising that with no correction for metabolic rate (creatinine),

**Table 4.** Relative activity catecholamine and indoleamine (mean and sd)

| Subjects | Measures | | |
|---|---|---|---|
| | DA/NA | HVA/MHPG | HVA/5HIAA |
| Psychosis | 23.1<br>32.1 | 5.6<br>6.7 | 6.2<br>10.8 |
| P-diag | 14.4<br>9.2 | 4.6<br>4.8 | 5.3<br>9.8 |
| NP-diag | 31.1<br>42.9 | **6.6**[3]<br>8.1 | 7.0<br>11.8 |
| P-symp | 13.6<br>8.6 | 3.7<br>3.2 | 4.7<br>9.2 |
| NP-symp | 31.9<br>42.7 | **7.4**[2]<br>8.5 | 7.9<br>12.5 |
| OCD | 25.9<br>40.4 | **9.1**[1]<br>10.8 | 3.5<br>3.9 |
| Controls | 16.7<br>14.9 | 3.4<br>2.4 | 10.9<br>19.7 |

1. $\mathbf{p < 0.013}$ t = + 2.60 OCD vs controls;
2. $\mathbf{p < 0.029}$ t = + 2.27 NP-symp vs controls;
3. $p < 0.065$ t = + 1.90 NP-diag vs controls

body area or quantity of urine that there were no group differences in the daily levels of NA, DA, 5 HT, MHPG, HVA or 5 HIAA ($F(12, 110) = 0.65$, $p < 0.8$; Mann-Whitney U = 85-136, z − 0.05/− 1.67, $p > 0.9$; Table 5).

However, with measures of concentration, neglecting metabolic rate but controlling for body size (i.e., units of $\mu g/l/m^2$), differences became more marked ($F(12, 110) = 2.4$, $p < 0.01$). Firstly there was the medication effect on psychotic patients - less DA, NA, HVA than OCD or controls ($0.05 < p < 0.001$, Scheffe) and less MHPG than controls. Secondly the unmedicated OCDs had higher concentrations of all substances than controls. These were significant for HVA ($p < 0.025$) and 5 HT ($p < 0.043$, Scheffe) confirming the results of measures taking creatinine metabolism into account.

### *Effect of age*

The only measure that tended to correlate with age in the controls was 5 HT utilization (Table 6). For OCDs correlations were evident in two of the three measures showing group differences: age related inversely to HVA and marginally to 5 HT levels. For psychotics age correlated inversely with MHPG and NA utilization. This largely reflected the inverse relationship in the two NP

**Table 5.** Daily quantitiy (μg/l) vs concentration (μg/l/m$^2$) of monoamines and metabolites (means)

| | DA | HVA | NA | MHPG | 5HT | 5HIAA |
|---|---|---|---|---|---|---|
| Psychotics | | | | | | |
| concen | **210**[1] | **1547**[2] | **14**[4] | **596**[5] | 42 | 1043 |
| per day | 553 | 3869 | 35 | 1769 | 107 | 2782 |
| OCDs | | | | | | |
| concen | 362 | **3952**[3] | 30 | 1031 | **169**[6] | 1671 |
| per day | 535 | 4033 | 36 | 1194 | 140 | 2076 |
| Controls | | | | | | |
| concen | 313 | 2578 | 24 | 975 | 75 | 1156 |
| per day | 520 | 4068 | 38 | 1550 | 116 | 1721 |

1. DA
   $p < 0.06$ Scheffe, U = 64 z − 2.51, **$p < 0.02$** M-W psychotics vs OCD;
   $p < 0.10$ Scheffe, U = 175 z − 2.98, **$p < 0.003$** M-W psychotics vs control;
2. HVA
   **$p < 0.001$** Scheffe, U = 53 z − 2.90, **$p < 0.004$ M-W psychotics vs OCD;**
   **$p < 0.04$** Scheffe, U = 198 z − 2.56, **$p < 0.011$** M-W psychotics vs control;
3. **$p < 0.03$** Scheffe, U = 87 z − 1.98, **$p < 0.05$** M-W OCD vs control;
4. NA
   **$p < 0.008$** Scheffe, U = 64 z − 2.52, **$p < 0.012$** M-W psychotics vs OCD;
   **$p < 0.04$** Scheffe, U = 154 z − 3.36, **$p < 0.001$** M-W psychotics vs control;
5. MHPG
   $p < 0.08$ Scheffe, U = 201 z − 2.50, **$p < 0.013$** M-W psychotics vs control;
6. 5HT
   **$p < 0.005$** Scheffe, U = 47 z − 3.00, **$p < 0.003$** M-W psychotics vs OCD;
   **$p < 0.05$** Scheffe, U = 105 z − 1.40, $p < 0.16$ M-W control vs OCD;
   $p < 0.52$ Scheffe, U = 193 z − 2.47, **$p < 0.014$** M-W psychotics vs control

groups *but* a positive correlation *with NA* in the two P groups. (This latter effect is evident in the negative relationship between age and DA/NA for P-groups). The trend for a negative correlation between age and 5 HIAA in the psychotics reflected largely the P-symp subgroup. (It can be seen that both P groups showed a positive relationship between age and the HVA/5 HIAA ratio).

### *Effect of symptom severity*

Did symptom severity play a role in these differences? Ratings were available for only a few OCDs, so we concentrate on BPRS scores: (sums of 7 point ratings divided by the number (18) of questions). The paranoid group was rated more ill (*P-diag* mean 3.5 sd 0.6, *P-symp* 3.3 sd 0.8 vs *NP-diag* 2.5 sd 0.9, *NP-symp* 2.5 sd 1.0).

BPRS scores correlated negatively with DA ($r = -0.48, p < 0.033$), MHPG ($r = -0.44, p < 0.05$) and DA/NA ratio ($r = -0.50, p < 0.026$). Correlations

**Table 6.** Significant pearson correlation coefficients for monoamine and metabolite measures with age within each group/subgroup of subjects

| Measure | Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | P-diag n = 12 | P-symp n = 12 | NP-diag n = 13 | NP-symp n = 13 | Psychosis n = 25 | OCD n = 11 | Control n = 27 |
| (Ad) | | | | | | | |
| (DA) | | | | | | | |
| HVA | | | | | | **− 0.88 p < 0.001** | |
| (DA util) | | | | | | | |
| NA | + 0.60 p < 0.04 | **+ 0.81 p < 0.001** | | | | | |
| MHPG | | | − 0.66 p < 0.02 | − 0.65 p < 0.02 | **− 0.51 p < 0.01** | | |
| NA util | | − 0.58 p < 0.05 | − 0.62 p < 0.03 | − 0.60 p < 0.03 | **− 0.57 p < 0.01** | | |
| 5HT | | | | | | − 0.72 p < 0.02 | |
| 5HIAA | | − 0.61 p < 0.04 | | | | − 0.43 p < 0.04 | |
| 5HT util | | | | | | | + 0.42 p < 0.03 |
| DA/NA | − 0.66 p < 0.02 | − 0.62 p < 0.04 | | | − 0.41 p < 0.04 | | |
| (HVA/MHPG) | | | | | | | |
| HVA/5HIAA | + 0.66 p < 0.02 | + 0.60 p < 0.04 | | | | | |

Measures exclude 2 psychotic subjects treated with NA antagonists: only measures attaining 5% significance are shown (a Bonferroni correction suggests setting alpha at 0.1–1%, see bold results)

were *not* seen with medication (r = + 0.28), prolactin (a measure of neuroleptic response, see discussion; r = + 0.25), other monoamine levels (e.g., HVA, r = + 0.02; NA r = − 0.12), utilization (e.g., 5 HT, r = − 0.18) or their concentration (e.g., 5 HT, r = + 0.16).

We caution that the correlations should be viewed as trends as the Bonferroni correction would reset alpha to 0.2%. The measures suggest that both DA and, relative to DA, NA levels decreased with increased severity. This would perhaps be expected as the P-diag group received more medication than the NP-diag group. However, as this medication difference did not hold for the P- or NP-

symp groups (Table 1) it is possible that illness severity and medication contribute separately to lower DA levels.

## Discussion

### *Main results*

The OCD patients excreted more AD and more of the dopamine metabolite HVA than healthy controls. As the concentration of HVA, not MHPG, and the HVA/MHPG ratio is higher, the implication of increased DA utilization is unlikely to reflect substantial changes in noradrenergic (NA) metabolism. OCD patients also excreted more serotonin (5 HT) than psychotic or healthy subjects.

For the psychotic patients depressed concentrations of DA, HVA and NA may be seen largely as effects of neuroleptic medication. The non-paranoid groups showed relatively high 5 HT utilization. This may partly reflect the illness and not be entirely a medication effect as 1) medication levels differed between NP-diag and NP-symp groups, 2) 3 NP patients were not on medication and, 3) BPRS ratings of symptom severity were similar between the groups. In contrast the increased level of DA utilization in the P-diag but not the P-symp group may largely reflect an unstabilized response to medication, as the former group was receiving higher doses of neuroleptics.

### *Changes in psychotic patients: medication, age and severity*

Paranoid patients showed a higher DA utilization than non-paranoids whose level approximated that of controls. This cannot have arisen from differences of NA utilization for the levels were similar between subgroups. This contrasts with a report of increased plasma MHPG in association with severe paranoid symptoms (Ko et al., 1988).

Could this have been a pure medication effect? We think not for two reasons: 1) the levels of medication (CPZ equivalents) were very similar between P-symp and NP-symp groups but were different between the P-diag and NP-diag groups; 2) the 3 patients without medication showed half the levels of the paranoid group (mean 7.7), but all were non-paranoid (the group with lower DA utilization).

Could the difference shown by paranoids have been one of typical vs atypical neuroleptic therapy? This also seems unlikely for two reasons. Firstly the 5 patients on clozapine were also the subjects whose group allegiance (P/NP) differed between diagnosis and symptom level. Secondly the 2 male patients on clozapine showed similar utilization levels to the 9 on butyrophenone treatment (15.6 vs 14.3). This lack of difference is striking in that levels of prolactin from these patients were, as expected, far higher after butyrophenone than after clozapine treatment (57 vs 15 ng/ml). Thus neither quantitative nor qualitative medication differences account adequately for the higher DA utilization in paranoid patients.

DA utilization did not correlate with age or symptom severity. But severity seemed to play a role in the neuroleptic effects seen, for the negative correlation with DA and MHPG levels suggests there was room for adjustment of pharmacotherapeutic treatment. (Indeed treatment levels for the P-diag group were arguably more appropriate for the P-symp group). Lastly the appearance of age correlations in measures showing group differences emphasizes that age is an important feature in deciding on a pharmacotherapeutic strategy. However, the age correlations did not significantly contribute to group differences as they were closely matched on this feature.

As we made an effort to conduct our measures as soon as practicable after admission of the patients (< 1 month) our finding increased DA utilization in the paranoid group may reflect numerous reports of a *reactive* response of plasma HVA to medication onset in those with a positive clinical response later (Chang et al., 1988; Mazure et al., 1991; Duncan et al., 1993). Responders are likely to include a high proportion of paranoid patients (Rettersol, 1991). But we should emphasize that our significant measure was HVA/DA; measures of HVA alone showed a similar but non-significant trend.

### *Changes in psychotic patients: an interpretation*

In accord with the hypothesis of Grace (1993) we think that positive paranoid symptoms reflect a potentiation of phasic DA activity, reflected here in increased utilization. Further, agents that exacerbate positive symptoms increase DA transmission and activity (Angrist et al., 1980). Thus we are observing a reflection of DA activity associated with paranoid symptoms that has not yet been stabilized through neuroleptic treatment.

In the NP-symp group DA levels tended to be higher. We also noted that 5 clozapine-treated patients changed group allegiance between subtyping by active symptoms and diagnosis. Together these support Grace's hypothesis (1993) that clozapine may be effective in non-paranoid psychotics by maintaining extracellular levels of DA in the face of depolarization block caused by the neuroleptic.

Lastly symptom severity was not related to 5 HT measures in psychotic patients. This supports our argument above for a qualitative relationship between 5 HT utilization and NP symptoms.

### *Changes in OCD patients*

We interpret the increases in OCD subjects of AD, 5 HT, HVA and general metabolic levels not in terms of stress but rather as reflecting an increased level of "activation". Animal studies of stress responses show decreased NA and increased NA, DA and 5 HT utilization (Heinsbroek et al., 1990). Of these only increased DA utilization applied to our OCD patients. Increased arousal is an appropriate description in the limited sense that increased adrenal production of cortisol, and here AD, is associated with OCD (Gehris et al., 1990). But

"activation", described as a state of readiness for targeting the outcomes of behaviour, has been associated with activity of the basal ganglia and DA systems (Pribram and McGuinness, 1993). Thus this concept would be supported by our and others' data on DA and neostriatal metabolism in OCD (Benkelfat et al., 1990; Swedo et al., 1992).

The absence of NA or MHPG differences in our OCD group implies that this transmitter has not contributed to DA metabolic measures, is itself unaffected in OCD and in view of NA associations with depression, that our subjects were not markedly depressed (Hollander et al., 1991; Swedo et al., 1992; Garvey et al., 1990).

OCD levels of 5 HIAA and especially 5 HT were raised compared to the healthy group, but utilization was unchanged. This implies that much 5 HT is synthesized and released but neither post- nor presynaptic uptake is taking place efficiently. Thus much 5 HT is excreted or partly metabolized and excreted. (The increase of 5 HIAA is unlikely to reflect transmission as this should result in inhibition of DA activity, which is not the case). This interpretation fits with reports of changes in OCD platelet uptake sites (a model for the CNS mechanism, Vitiello et al., 1991; Bastani et al., 1991).

Unresolved remains the puzzle as to why more 5 HT transmission is not occurring. Presumably this reflects an insufficiency of the second messenger system which may, in part, be overcome if much more 5 HT is released as a result of treatment with uptake-blockers. But this also points to the limits for therapy with this pharmacologic strategy. Our data showed that this imbalance in 5 HT and HVA was more severe in the younger patients.

We conclude that analysis of urinary excretion of transmitters and their metabolites can offer a general guide to the state of activity in monoamine systems in individuals. This can be useful for assessing the state of patients with and without medication and offer guidance to improvements of pharmacotherapeutic treatment.

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