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ORIGINAL PAPER

Plasma Homovanillic Acid and Prolactin in Huntington's Disease

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Abstract Dopaminergic activity is expected to be altered in patients with Huntington's disease (HD) and be related to factors like duration and severity of illness or patients' specific symptomatology like dementia, depression, or psychotic features. We assessed plasma homovanillic acid (pHVA) and plasma prolactin (pPRL), two correlates of dopaminergic activity, in 116 subjects with CAG repeats expansion in the HD gene, 26 presymptomatic (18 females) and 90 with overt symptomatology (43 females). Patients were evaluated using the Unified HD Rating Scale and the Total Functional Capacity Scale. Presence of dementia, depression, and psychotic features were also assessed. The age range of the patients was 22–83 years, duration of illness from 0.5 to 27 years, and CAG repeat number from 34 to 66. A group of 60 age and sex matched healthy subjects served as control group. Plasma PRL in subjects at risk and in neuroleptic-free patients, evaluated separately for males and females, did not differ from controls. Plasma HVA levels did not differ from controls in the group of presymptomatic subjects, but were significantly higher in the patients group. This increase was positively associated mainly with severity of illness and functional capacity of the patients, and not with presence of depression or dementia. Plasma HVA levels may be proven to be a peripheral index of disease progression. Reducing dopaminergic activity may have not only symptomatic, but also neuroprotective effects in HD.

Keywords Huntington's disease · Severity of illness · Plasma homovanillic acid · Prolactin

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Introduction

Altered dopaminergic neurotransmission has been implicated in Huntington's disease (HD) for several reasons. The hyperkinetic symptoms, as well as the psychotic features, have been ascribed to an increased dopaminergic activity, caused either by excessive dopamine release or hypersensitive post-synaptic dopamine receptors. On the other hand, dopamine or its metabolites have been discussed as potential neurotoxic agents that may contribute to neuronal cell death [1, 2]. Striatal neurons from transgenic mice with CAG repeat expansion have been shown to exhibit elevated cell death on exposure to neurotoxic concentrations of dopamine [3].

Dopamine turnover in HD may be influenced by many factors. Loss of inhibitory GABAergic neurons may cause dopaminergic activation, while loss of dopaminergic receptors may lead to compensatory hyperactivity in the remaining neurons. The process seems to begin in asymptomatic gene carriers, and intensify with the progression of the illness. Altered dopamine turnover may thus be related to duration of illness, severity of illness, or specific symptomatology common in HD patients, like presence of dementia, depression, and psychotic features.

Binding studies revealed a reduction of dopamine receptors in striatum of HD patients [4–6]. Ginovant et al. [7], measuring raclopride binding with PET techniques, reported a D2 dopamine receptor loss in HD patients that correlated to the CAG repeat number in the Huntington gene. A 4% annual loss in striatal dopamine receptor binding was found using [^{11}C] raclopride-PET in asymptomatic Huntington's disease mutation carriers, in a follow-up for 40 months, and 6.5% in patients with active progression of the disease [8].

Measurements of dopamine and/or its main metabolite homovanillic acid (HVA) in post-mortem brain tissue,

however, have given conflicting results: Mann et al. [9] found normal HVA, Reynolds and Garrett [10] normal dopamine and reduced HVA, Kish et al. [11] reduced dopamine and HVA. Most of the studies measuring HVA in CSF of patients with Huntington's disease indicate reduced dopamine turnover [12, 13], although normal levels of CSF HVA have been also reported [14].

Aside from central dopaminergic turnover, HVA can be built in several sites of the body. In the periphery it can be built from the catabolism of dopamine that has not been converted to noradrenaline in sympathetic neurons [15, 16], and the portion of pHVA deriving from brain is considered to be about 30% [17]. Most of the central contribution to plasma HVA though seems to originate from subcortical dopaminergic neurons, and not from cerebrovascular sympathetic neurons [18].

Evidence has accumulated from numerous studies of patients with neurologic or psychiatric diseases that pHVA levels are associated to various aspects of central dopaminergic processes. In schizophrenia, pHVA levels were found to predict severity of symptoms and response to neuroleptics [19–24], indicating that it may reflect central processes [25]. Low pHVA levels were associated with greater improvement in verbal memory in schizophrenic patients during treatment with clozapine [26]; a decline in verbal episodic memory was recently reported in presymptomatic subjects with the HD CAG expansion [27].

Sweet et al. [28] reported associations of pHVA to parkinsonian rigidity and behavioral symptoms in patients with dementia. Recently, elevated pHVA levels compared to age matched normal controls were reported in a group of 17 delirious patients with Alzheimer's disease but not in non-delirious patients [29], and the authors suggest increased central dopaminergic turnover related to delirium.

Interestingly, pHVA was found to increase together with dopamine transporter SPECT measures during cocaine withdrawal, so that it was suggested that pHVA may reflect striatal dopamine receptor density [30]. Moreover, plasma levels of HVA were found to correlate significantly to cisternal HVA levels in a group of 18 neurologic and psychiatric patients [31], so that the question of how far pHVA reflects central dopaminergic activities is still open. In relation to HD, plasma HVA has not been studied until now.

In this study, we estimated plasma levels of HVA in subjects with the pathological expansion of CAG repeats in the Huntington gene, before or after the disease onset. We searched for differences from a group of healthy controls, as well as for relations of HVA levels to duration, severity, and symptomatology of illness. In addition, we estimated plasma prolactin levels (pPRL), as a second index of hypothalamic-pituitary dopaminergic activity, since dopamine is the main factor regulating prolactin release from pituitary lactotrophs.

Subjects and Methods

Ninety patients with HD (47 males) and 26 subjects at risk (8 males) were studied. They were outpatients (new patients or patients in follow-up) of the Athens University Neurologic Clinic, Eginition Hospital.

The ages of the patients ranged from 22 to 83 years (mean ± SD = 50.7 ± 13.2), age at onset ranged from 19 to 73 years (44.4 ± 11.6), and duration of illness from 0.5 to 27 years (6.3 ± 6.4). Their CAG repeats numbers ranged from 34 to 66 (45.2 ± 5.1). The ages of the subjects at risk ranged from 18 to 77 years (33.6 ± 13.1), and their CAG repeats number from 34 to 53 (43.4 ± 4.7). A control group was built from 60 healthy subjects in the same age range (27–74 years) and same male to female ratio (33 males).

For the evaluation of disease symptomatology we used the Unified Huntington's Disease Rating Scale (UHDRS, Huntington Study Group [32]). In addition, we evaluated each patient for the presence of dementia (cutoff point 25 in the Mini-Mental State Examination), hyperkinesias, depression (cutoff point 6 in the four items evaluating mood in the behavior assessment of the UHDRS), and psychotic features. The severity of the illness was assessed according to the HD Total Functional Capacity Scale score of Shoulson and Fahn [33]. Patients were classified in degrees of severity, according to their ability to cope with demands of daily life. In first degree (mild), patients are still fully able to carry on their domestic and professional activities. In second degree (moderate) they have given up professional activities, but are still independent at home, and in third degree (severe) patients are dependent even for their daily demands.

Genomic DNA was extracted from blood using standard salting-out methods. Subjects' DNA was typed according to the method of Warner et al. [34], to assess directly the number of CAG units at 5′ of the Huntington gene (IT-15).

For the estimation of pHVA and pPRL, a blood sample was taken from each subject between 08:00 and 11:00 h in EDTA tubes. The majority of patients were on follow-up and blood samples were taken after an overnight fast and abstaining from smoking and coffee intake. Plasma was separated by centrifugation and stored at −30°C until estimations.

Plasma HVA was estimated by high-pressure liquid chromatography with electrochemical detector. For each estimation, a 0.5 ml plasma aliquot and a second one in which 10 ng pure HVA were added were acidified by the addition of 0.5 ml HCl 1N, and extracted into ether. After evaporation of the ether with nitrogen flow, the residue was dissolved in mobile phase, and injected in the HPLC-system. The differences in peak height of plasma with and plasma without standard, corresponding to 20 ng/ml HVA,

were used for calculation of the unknown metabolite concentration. In this way, the possible differences in extraction yield of the plasma samples are compensated, and the coefficients of variation were kept below 10%. Prolactin was estimated in plasma using the radioimmunoassay kits of Adaltis (Casalecchio di Reno, Italy), with coefficients of variation not more than 5%.

For the comparison of the data among groups we used analysis of variance, with covariates as appropriate, followed by planned or post-hoc comparisons. For the relations among variables we used Pearson and Spearman correlation coefficient tests. Multiple regression analyses were performed for the group of patients with independent variable pHVA or pPRL, and dependent variables sex, age, age at onset, duration of illness, presence of dementia, depression, and psychotic features. Ridge regression was used to control for multicollinearity, since relations between the dependent variables are expected.

One of the objectives of the study was to investigate possible relations of dopamine metabolism to disease progression. To this, we had to include patients with moderate and severe symptomatology who are usually under chronic treatment with haloperidol. Sixteen patients in follow up were on treatment with haloperidol, usually in low doses of 2–5 mg per day, and we decided to include them in the analysis because: (a) data from the literature show that pHVA levels are not considerably influenced by chronic treatment with haloperidol: Zumarraga et al. [35] observed a 15% reduction in pHVA after treatment of a large number of schizophrenic patients with a mean dose of 10 mg daily haloperidol for a month, while Labarca et al. [36] reported no change in pHVA levels of 15 naïve schizophrenic patients treated with 5 mg haloperidol for 5 weeks; (b) when patients with moderate or severe symptomatology were compared, 16 on treatment with haloperidol and 40 untreated, there were no differences in pHVA levels, and (c) although pPRL levels were elevated in the treated group, there was no correlation between pPRL and pHVA plasma levels. Moreover, treatment was considered as dependent variable in the multiple regression analysis searching for associations of pHVA or pPRL to clinical features of the patients.

Results

The number of male and female subjects in the control group was in analogy to the patients' group (ratio males to females 1.22 and 1.27, respectively). The mean values were 10.74 ± 3.9 for males and 11. ± 4.1 for females in the control group ($F = 0.29$, d.f. = 1, 58, $P = 0.59$), and 12.8 ± 7.5 for males and 12.8 ± 6.7 for females in the patients group ($F = 0.00$, d.f. = 1, 65, $P = 0.99$). No differences in pHVA between sexes in healthy subjects have been also previously reported, i.e. by Zhang et al. [37] for 32 males and 30 females. Consequently, gender was not considered as a variable in the analysis for pHVA.

Table 1 Mean values, standard deviations, and range of age, CAG repeats number, duration of illness, and scores in the Unified Huntington's Disease Rating Scale of the 90 HD patients

Variable	Mean ± SD	Range	Rs	*P*
Age	50.7 ± 13.2	22–83	0.466	0.001
CAG repeats number	45.2 ± 5.1	34–66	−0.368	0.001
Duration of illness, years	6.3 ± 6.4	0.5–27	0.406	0.001
Total Motor Score	46.3 ± 29.0	6–104	0.221	0.03
Maximal Chorea Score	13.2 ± 7.3	3–27	0.196	0.06
Verbal Fluency Test	28.2 ± 14.1	5–48	−0.139	0.19
Symbol Digit Modality Test	25.3 ± 11.4	6–43	−0.159	0.13
Stroop Interference Test	27.6 ± 8.9	12–40	−0.145	0.17
Total Behavior Score	22.8 ± 13.2	2–46	0.218	0.04
Functional Checklist Score	13.6 ± 6.2	3–24	−0.236	0.02
Independence Scale %	60.2 ± 24.1	20–100	−0.203	0.054
Total Functional Capacity	6.3 ± 3.4	1–12	−0.265	0.011

The Spearman correlation coefficients (Rs) to pHVA levels and their significance (*P* value) are also given

The clinical data and the scores in the subscales of the Unified Huntington's Disease Rating Scale for the 90 HD patients are shown in Table 1, where also the non-parametric Spearman correlation coefficients of the subscale score to pHVA levels are mentioned.

The mean values of age, pHVA, and pPRL of patients, subjects at risk, and controls are shown in Table 2. Analyses of variance with age as covariate showed significant differences in pHVA levels among groups. Planned comparisons showed that for subjects at risk the levels were not different from controls, while they were significantly higher for the group of patients. The elevated PRL levels of the patients group are clearly due to haloperidol treatment and are not related to the disease. Indeed, when we analyzed pPRL levels of the control subjects, subjects at risk, and patients separately for males and for females, including in the patients group only subjects not taking haloperidol, the differences in pPRL were not significant (Table 2).

We analyzed further pHVA levels of the patients in relation to severity of illness categorized according to the Total Functional Capacity Scale of Shoulson and Fahn [33]. There were 34 patients with severity grade I (mild), 30 patients with grade II (moderate), and 26 patients with grade III (severe). Duration of illness in the third group was significantly longer than in the other two groups. Thus, duration of illness was used as covariate in the ANOVA, together with age. The results are shown in Table 3. Plasma HVA levels were significantly higher in patients

Table 2 Plasma levels of homovanillic acid (pHVA) and prolactin (mean ± SD, in ng/ml) of control subjects, subjects at risk for HD, and patients with Huntington disease (47 males), 17 on treatment with low doses haloperidol

Group	*N*	Age	pHVA	pPRL	Males		Females	
					N	pPRL	*N*	pPRL
Controls	60	47.5 ± 10.8	10.7 ± 4.9	6.9 ± 3.1	33	6.04 ± 2.61	27	7.99 ± 3.46
Subjects at risk	26	33.7 ± 13.1	11.1 ± 4.5	8.2 ± 3.5	8	6.44 ± 1.58	18	9.04 ± 3.84
Patients	90	50.7 ± 13.1	13.6 ± 7.0*	13.8 ± 16.3*	41	6.86 ± 3.51	32	9.25 ± 4.21
F			3.83	5.14		0.62		0.99
P			0.024	0.007		0.54		0.37

Prolactin levels of males and females in the groups of controls, subjects at risk, and *neuroleptic-free* patients are also given and compared. Statistical evaluation by ANOVA with age as covariate, followed by planned comparisons

* $P < 0.01$ compared to controls (planned comparisons)

Table 3 Comparison of plasma homovanillic acid and plasma prolactin levels of subgroups of patients according to severity of illness as measured by the Total Functional Capacity Scale (Shoulson)

Severity of illness	*N*	Age	Duration of illness	pHVA (ng/ml)
Mild	34	47.0 ± 12.3	3.3 ± 4.5	11.4 ± 4.9
Moderate	30	49.4 ± 12.1	5.1 ± 4.9	12.1 ± 6.3
Severe	26	57.0 ± 13.7	11.6 ± 6.8	18.2 ± 8.1
$F_{2, 85}$				3.45
P				.036

Planned comparisons	*F*	*P*
Mild versus moderate	0.01	.92
Mild versus severe	5.67	.019
Moderate versus severe	5.73	.019

Statistical evaluation by ANOVA with age and duration of illness as covariates

with severity grade III compared to patients with grade I ($P = 0.02$) or grade II ($P = 0.02$, Table 3). Compared with controls, only the subgroup of patients with severity grade III had significantly elevated pHVA levels.

Plasma HVA levels were not correlated to age in the group of controls ($r = 0.0513$, $P = 0.66$), or in the group of subjects at risk ($r = 0.2765$, $P = 0.17$). A significant correlation was found in the patients' group ($r = 0.4174$, $P < 0.001$), which is rather due to the increasing severity of illness with duration and age than to age per se.

We further performed multiple regression analyses, with dependent variables pHVA or pPRL, and independent variables sex, age, duration of illness, severity of illness, presence of dementia, of depression, and of psychotic features, as well as treatment with haloperidol. Plasma HVA levels were significantly associated only to age and severity of illness, while pPRL levels were significantly related to sex, duration of illness, and treatment (Table 4).

According to these results, treatment with haloperidol was a significant predicting factor for pPRL, but not for

Table 4 Results of two multiple regression analyses (ridge regression) with dependent variables either plasma levels of homovanillic acid (pHVA) or of prolactin (pPRL), and independent variables sex, age, duration of illness, severity of illness, presence of dementia, of depression, and of psychotic features, and treatment with haloperidol in 90 patients with HD (17 on treatment)

	pHVA		pPRL	
Multiple R	0.5426		0.7950	
$F_{8, 81}$	4.22		17.38	
P	0.0003		0.00001	
Variable	Beta	*P*	Beta	*P*
Sex	0.098	0.31	0.191	0.007
Age	0.247	0.017	−0.92	0.21
Duration of illness	0.139	0.21	0.314	0.0002
Severity of illness	0.336	0.005	0.073	0.39
Dementia	−0.092	0.38	−0.027	0.72
Depression	0.073	0.47	0.031	0.67
Psychotisism	−0.080	0.43	−0.033	0.65
Treatment with haloperidol	−0.081	0.43	0.554	0.00001

pHVA. Since there is always a question about the influence of the dopamine receptor blocker haloperidol on dopamine turnover, we further examined this possibility in our sample by comparing pHVA of the subgroup of patients on treatment with haloperidol to the neuroleptic-free subgroup. Patients on treatment were—except one patient—of severity grade II or III, so we took for comparison only the drug-free patients with severity grade II or III. The results of the ANOVA with covariates age and duration of illness showed highly significant increases in pPRL, but no differences in pHVA (Table 5).

Discussion

Plasma HVA levels of the group of 28 patients with mild symptomatology were not different from controls, and this

Table 5 Effect of haloperidol treatment on plasma homovanillic acid and prolactin levels

Haloperidol treatment	*N*	Age	Duration	pHVA	pPRL
No	40	50.5 ± 13.1	6.7 ± 5.8	14.2 ± 7.8	8.1 ± 4.1
Yes	16	58.9 ± 12.0	11.8 ± 7.4	16.6 ± 7.7	40.0 ± 24.5
ANOVA, covariates age, duration of illness					
$F_{1, 52}$				0.02	53.15
P				0.89	.0001

Patients on haloperidol with moderate or severe symptomatology are compared with patients with moderate or severe symptomatology not on haloperidol. Differences are significant only for prolactin

is in agreement with some studies where normal HVA levels were found in CSF of patients with HD in the early stage of the illness [14].

The results of the present study show that dopaminergic activity increases considerably with worsening of the symptoms. This has to be seen in relation to the neurotoxic effects of dopamine on neurons with mutated huntingtin, since accelerated dopamine turnover may contribute to disease progression [1–3].

A correlation of pHVA to the age was not found in our group of normals, covering the same broad age range (27–74 years, Rs = 0.100, n.s.). Plasma HVA is high in the early days of life and declines with age [38], but in adult population no significant correlation to age has been reported. No correlation of pHVA to age was found in a population of 72 schizophrenic patients in the age range of 20–50 years [39]. In our patients, age correlated to duration of illness, as well as to age at onset. The positive correlation of pHVA to age in our patients' group can be attributed to the increased severity of the symptoms with age, and not to age per se.

In the degree that pHVA reflects the turnover of striatal dopamine, the results of the present study indicate that it increases with disease progression, and reaches significantly increased levels in patients with severe HD symptomatology. Since it has been repeatedly found that in HD there is a loss of dopaminergic receptors especially in striatum, an increased dopaminergic turnover can be understood as a compensatory mechanism of increased production and release of dopamine in the intact presynaptic neurons. Nevertheless, if the neurotoxic effects of dopamine to neurons with the Huntington mutation gene are considered, an increase in dopamine turnover may precede receptor loss, creating thus a vicious cycle. From the regression line of the correlation between pHVA and duration of illness, a 6.1% mean annual increase in pHVA is calculated, which is in good agreement with the calculated 6.3% [40] and 6.5% [8] mean annual loss with disease progression in striatal dopamine receptor binding in HD patients, so that an interconnection of the two indexes can be assumed. This will support the possibility that pHVA levels are related to striatal dopaminergic activity, as has been indicated by Bowers et al. [30], who found a positive correlation between pHVA levels and dopamine transporter density, which depends on presynaptic dopaminergic activity. Plasma HVA levels may thus be a candidate for a peripheral index of disease progression in HD.

Dopaminergic signaling is considered to participate in striatal neurodegeneration, and mechanisms to explain its action have been proposed by Tang et al. [41]. The authors suggest that dopamine pathway inhibitors should be considered as neuroprotective agents, and not only for symptomatic treatment in HD. The increased pHVA levels with severity of illness, as well as the apparent lack of increases in dopamine turnover by haloperidol found in the present study, are in line with their hypothesis.

A methodological limitation of the study is that blood samples, taken all at the same time interval, i.e. between 08:00 and 11:00 h, were not taken from all subjects following strict conditions proposed by some authors, namely after 12 h of fasting, no smoking, and after a half hour rest. This was done for the majority of cases in the three groups studied and may have not influenced the differences found between groups.

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