Neuroendocrine evidence of normal hypothalamus-pituitary dopaminergic function in Huntington's disease

Manolis Markianos, Marios Panas, Nikos Kalfakis, John Hatzimanolis, Dimitrios Vassilopoulos

Athens University Medical School, Department of Neurology, Eginition Hospital, Athens, Greece

Correspondence to: Dr. Manolis Markianos
Athens University Medical School
Department of Neurology, Eginition Hospital
Vas. Sophias 74, Athens 11528, Greece.
TEL: +30-2107289266; FAX: +30-2107216474; E-MAIL: markian@otenet.gr

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Abstract

OBJECTIVES: In addition to neuronal loss in striatum and cerebral cortex that characterizes Huntington's disease (HD), hypothalamic atrophy has also been found only in certain areas, probably not including dopaminergic functions.
METHODS: We assessed the reactivity of the hypothalamus-pituitary dopaminergic system by measuring the acute prolactin (PRL) responses to 5 mg i.m. haloperidol in male and female HD patients and in female subjects with expanded CAG repeats in the Huntington gene before disease onset, as well as in a group of healthy males.
RESULTS: The responses of the male patients were similar to those of a group of male healthy volunteers. Females gave higher PRL responses, with no differences in the response patterns of female patients and females at risk for HD. PRL elevations were not related to severity of illness, or to presence of dementia, depression, or psychotic features.
CONCLUSIONS: The results implicate a normal dopaminergic input from hypothalamus to pituitary and preserved pituitary dopamine receptors, indicating that hypothalamic atrophy in HD does not affect mechanisms involved in PRL secretion by haloperidol.

ORIGINAL ARTICLE

INTRODUCTION

The main finding on Huntington's disease (HD) neuropathology shows a severe neuronal loss in striatum and cerebral cortex (Vonsattel et al. 1985). Affected are primarily striatal spiny neurons expressing dopamine receptors, while the presynaptic dopaminergic system is not involved (Reiner et al. 1988). Loss of dopaminergic receptors have been reported in postmortem human caudate nucleus by measuring receptor mRNA (Augood et al. 1997), in human striatum by positron emission tomography (Weeks et al. 1996), and in striatum and cortex of transgenic mice with an abnormal human Huntington gene (Cha et al. 1998).

Possible alterations either in the hypothalamic dopaminergic input to pituitary, or in the pituitary dopamine receptors, would lead in changes at least in prolactin secretion from the anterior pituitary, since the secretion is under tonic inhibition of hypothalamic dopamine (for review see Freeman et al. 2000). In addition, hypothalamic atrophy

also occurs, with neuronal loss in the lateral tuberal nucleus (Kremer et al. 1990; Kassubek et al. 2004), and in neurons expressing orexin (Petersen et al. 2005).

Most previous studies did not find any abnormalities of PRL secretion in HD. Murri et al. (1980) measured nocturnal PRL secretion in six HD patients and found no differences in the secretory pattern from age-matched control subjects. Lavin et al. (1981) found no differences from controls either in baseline, or in the responses of PRL or TSH to thyrotrophin releasing hormone (TRH) in eight patients with HD. Durso et al. (1983) studied PRL levels every 30 minutes for 24 hours in nine female patients with HD, and found no differences from controls. In contrast, Hayden et al. (1977) had previously reported low basal PRL and impaired responses to chlorpromazine and to TRH in eight HD patients, while in first-degree relatives, 11 had normal responses, seven exaggerated, and five impaired. As Petersen and Bjorkqvist (2006) mention in their review article on hypothalamic endocrine aspects in HD, no conclusions can be drawn from these conflicting results.

Hypothalamic dopamine exerts its inhibitory action on D2 dopamine receptors located on lactotrophs (Caron et al. 1978). Acute administration of haloperidol causes robust elevations in plasma PRL (Gruen et al. 1978), by blocking D2 dopamine receptors and thus withdrawing the inhibitory action of dopamine. The magnitude of the increases is taken as a measure of D2 receptor responsivity, a combination of their number and activation state. The PRL responses to haloperidol is a measure of the degree of dopaminergic receptor blockade by different neuroleptic drugs (Markianos et al. 2001).

In this study we assessed the functional capacity of the hypothalamic-hypophysial dopaminergic system by measuring prolactin increases after a haloperidol challenge test in patients with pathological CAG repeats number in the Huntington gene, before or after disease onset. We searched for differences from normal controls, and for relations of the prolactin responses to clinical features of the patients.

PATIENTS AND METHODS

Twenty-four male and thirteen female patients with overt HD symptomatology and eight female subjects at risk for HD were studied. The patients were all in follow-up, and only patients who were not taking any neuroleptic drugs were included in the study. Their CAG repeats number varied from 40 to 66 (mean 46±7). The age of the patients ranged from 22 to 68 years (mean 46.5±12.6), age at onset varied from 19 to 63 years (mean 41.7±11.6), and duration of illness from 0.5 to 23 years (mean 4.8±5.1). The age of females at risk for developing the disease varied from 29 to 48 years and their CAG repeats number from 40 to 47. We also performed the haloperidol test in 17 male healthy volunteers, aged 21 to 50 years (mean 30.9±0.8). We did not perform the test in healthy female subjects, so we have no data for PRL responses to haloperidol for healthy females. The PRL responses of the female patients were compared only to the responses of females at risk for HD.

For the evaluation of the disease symptomatology we used the Unified Huntington's Disease Rating Scale (UHDRS, Huntington Study Group, 1996). 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 (1979). Patients were classified in degrees of severity, according to their ability to cope with demands of daily life. In the first degree (mild), patients are still fully able to carry on their domestic and professional activities. In the second degree (moderate) they have given up professional activities, but are still independent at home, and in the third degree (severe) patients are dependent even for their daily demands.

The haloperidol challenge test was performed beginning at 0900–1000 hours. After taking a baseline blood sample, 5 mg haloperidol were injected intramuscularly, and further blood samples were taken at times 30, 60, 90, and 120 minutes. Plasma was separated by centrifugation and kept at –30 °C until estimation. Prolactin was estimated in plasma using the radioimmunoassay kits of Adaltis (Casalecchio di Reno, Italy), with coefficients of variation for duplicates not more than 5%. Prolactin levels were expressed in ng/ml plasma.

The response of each subject to the haloperidol challenge test was calculated as the difference of the maximal post-haloperidol PRL value, usually that of the 90-min sample, from baseline value (DPRLmax).

Genomic DNA was extracted from blood using standard salting-out methods. Subjects' DNA was typed according to the method of Warner et al. (1993), to assess directly the number of CAG units at 5' of the Huntington gene (IT-15).

For comparison of the PRL response patterns between groups we used analysis of variance for repeated measures with covariates age and body weight (ANCOVAR). ANCOVA was also used in evaluating DPRLmax of subgroups of patients with mild, moderate, or severe symptomatology. DPRLmax were compared to clinical variables using the Spearman's rank correlation test.

RESULTS

The mean values of age, body weight, baseline PRL and maximal PRL response to haloperidol are mentioned in the Table 1, while the patterns of PRL levels during the haloperidol challenge test in the four groups studied are shown in the Figure 1.

PRL responses to haloperidol were, as expected, higher in females, and the patterns of PRL levels during

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Tab. 1. Mean values (±SD) of age, body weight, baseline prolactin, maximal prolactin response to 5 mg haloperidol i.m. (DPRLmax), and CAG repeats number of the groups studied. The results of ANCOVA with covariates age and body weight are given.

GROUP	N	AGE	Weight	Baseline PRL	DPRLmax	CAG
Male controls	17	30.9±9.8	79.1±11.4	6.68±1.96	49.8±21.2	
Male patients	24	46.5±12.6	70.9±5.9	6.99±3.91	44.8±23.6	41 - 66
F (df=1, 37)				0.12	0.13	
p-value				0.73	0.72	
Females, at risk	8	37.3±7.6	64.4±15.7	10.9±6.4	110.4±44.3	40 - 47
Female patients	13	46.7±13.1	57.0±6.8	8.84±3.9	196.1±59.5	41-62
F (df=1, 17)				2.82	0.96	
p-value				0.07	0.34	

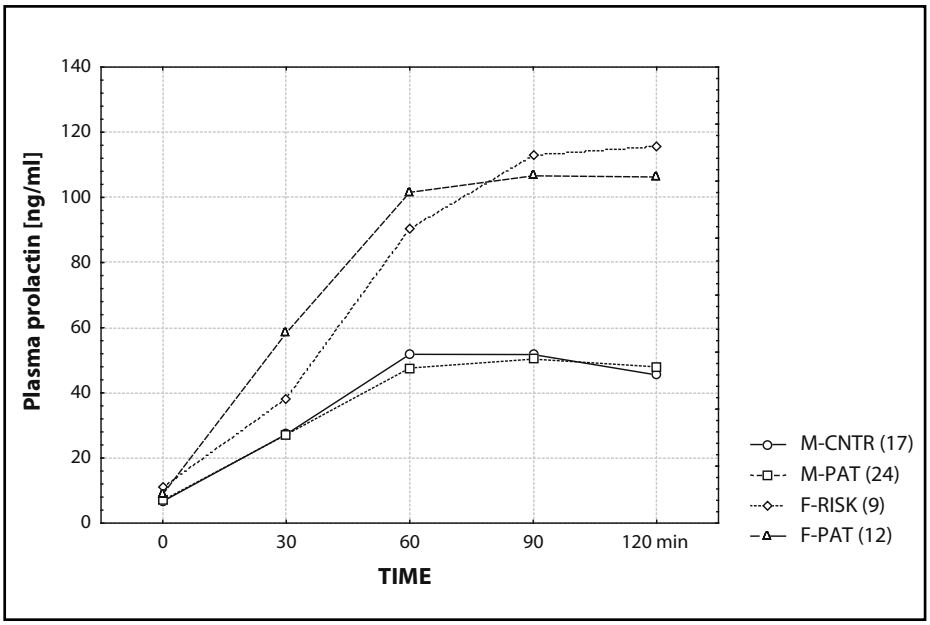

Fig. 1. Mean values of plasma prolactin levels after administration of 5 mg haloperidol i.m. in male healthy controls, male HD patients, females at risk for HD, and female HD patients. Number of subjects in parentheses.

the haloperidol test were evaluated separately for males and females, using analysis of variance for repeated measures with age and body weight as covariates. No group effect was found either for males (p=0.79) or for females (p=0.22), highly significant time effect for both genders (p<0.0001), and no group versus time interaction, either for male controls versus male patients (F=0.46, p=0.77), or for females at risk and female patients (F=0.94, p=0.45).

Baseline PRL levels were evaluated only for male patients, and no significant differences were found compared to male controls (ANOVA, F=0.09, p=0.76).

Regarding severity of illness, from a total of 37 patients, 16 (7 females) had mild symptomatology, 14 (4 females) moderate, and 7 (2 females) severe. There were no significant differences of PRL responses to haloperidol between groups, either for males (F=0.47, p=0.63) or for females (F=1.95, p=0.19). Negative results were also obtained when the responses of subgroups of male or female patients were compared, with or without dementia, depression, or psychotic features.

Maximal PRL responses to haloperidol were not related to age, duration of illness, body weight, or CAG repeat number either in male or in female patients.

DISCUSSION

The results of the study, i.e. normal PRL responses to the acute administration of haloperidol, indicate that the hypothalamus – pituitary dopaminergic system is well functioning in patients with HD. This is in accordance with the results of Reiner et al. (1988) who found that presynaptic dopaminergic neurons are not involved in HD pathology. The preserved presynaptic dopaminergic hypothalamic neurons release dopamine, which reaches through the portal vessels the pituitary ante-

rior lobe and exerts the tonic inhibition on PRL release (Leong et al. 1982). Preserved seem to be also the D2 dopamine receptors in pituitary lactotrophs, since they react normal to their blockade by haloperidol.

Mutant huntingtin is expressed in the brain and many tissues of the body (Strong et al. 1993), its degenerative action, though, is limited in cells that show a specific vulnerability. In HD, while the spiny GABAergic neurons degenerate, striatal interneurons are spared (Ferrante et al. 1985). Differences in resistance to neurodegeneration have been ascribed to transcriptional dysregulation, but the expression of certain proteins that may have a protective role has also been reported (Zucker et al. 2005). The documented pathology of hypothalamus and endocrine system in HD (Petersen and Bjorkvist 2006) seems not to include the mechanisms of PRL secretion, and to be specific for certain cell populations.

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