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Decreased Vesicular Storage and Aldehyde Dehydrogenase Activity in Multiple System Atrophy

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Abstract

Background—Parkinson disease (PD) and multiple system atrophy (MSA) share some neuropathologic findings (nigrostriatal dopaminergic lesion, alpha-synuclein deposition) but not others (Lewy bodies in PD, glial cytoplasmic inclusions in MSA). In PD evidence has accrued for a vesicular storage defect and aldehyde dehydrogenase (ALDH) inhibition in residual dopaminergic terminals, resulting in accumulation of the toxic dopamine (DA) metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL). In this study we asked whether MSA entails a similar abnormal neurochemical pattern.

Methods—DA and its main neuronal metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), norepinephrine (NE) and its main neuronal metabolite 3,4-dihydroxyphenylglycol (DHPG), the catecholamine precursor DOPA, and DOPAL were measured in striatal and frontal cortical tissue from patients with pathologically proven end-stage MSA (N=15), sporadic PD (N=17), and control subjects (N=18).

Results—Compared to the control group, the MSA and PD groups had similarly decreased putamen DA (by 96% and 93%, $p<0.0001$), DOPAC (97% and 95%, $p<0.0001$), NE (91% and 74%, $p<0.0001$), and DHPG (81% and 74%, $p<0.0001$). In the MSA and PD groups, ratios of DOPAL:DA were 2.3 and 3.5 times control and DHPG:NE 3.1 and 2.6 times control, while DOPAC:DOPAL ratios were decreased by 61% and 74%. In both diseases cortical NE and DHPG were decreased, while DA and DOPAC were not.

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Conclusions—MSA and PD entail a catecholamine metabolic profile indicating impaired vesicular storage, decreased ALDH activity, and DOPAL buildup, which may be part of a common pathway in catecholamine neuronal death. Targeting this pathway by interfering with catecholaldehyde production or effects constitutes a novel treatment approach.

Keywords

Multiple system atrophy; Parkinson disease; Putamen; Dopamine; Norepinephrine; DOPAL

INTRODUCTION

Multiple system atrophy (MSA) is a progressive neurodegenerative disease manifested by chronic autonomic failure coupled with Parkinsonism, cerebellar ataxia, or both. MSA is characterized by glial cytoplasmic inclusions [1], which contain abundant alpha-synuclein [2]. In Parkinson disease (PD) alpha-synuclein is deposited in neurons in Lewy bodies [3]. Both diseases therefore are synucleinopathies, although the overall burden of synuclein deposition in the brain is far greater in MSA [4].

The differential diagnosis of MSA vs. PD can be difficult during life [5, 6] and is established definitively only by autopsy. MSA is uncommon, underdiagnosed [7, 8], and understudied. Based on PubMed searches MSA is far less intensively researched than is PD (4,558 vs. 56,198 listings as of this writing).

Both MSA and PD involve striatal dopamine (DA) depletion, especially in the putamen [4, 9]. The severity of the depletion in PD is greater than can be explained by loss of substantia nigra dopaminergic neurons [10] or of dopaminergic terminals [11]. Recent post-mortem and in vivo data have indicated that in the putamen and heart in PD there is substantially decreased vesicular sequestration of cytoplasmic catecholamines in the residual terminals [12-14]. In both regions denervation and the vesicular storage defect contribute about equally to the depletion of transmitter stores.

Decreased vesicular sequestration would be expected to shift the fate of intra-neuronal DA toward enzymatic deamination catalyzed by monoamine oxidase-A in the outer mitochondrial membrane (Figure 1). The immediate product of this deamination is the catecholaldehyde 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is potentially toxic, via cross-linking with various proteins [15], increased production of reactive oxygen species [16], and oligomerization of alpha-synuclein [17-19]. Normally DOPAL is detoxified by aldehyde dehydrogenase (ALDH) to form 3,4-dihydroxyphenylacetic acid (DOPAC); however, in PD there is decreased ALDH activity in putamen [12]. The concept has emerged that DOPAL and alpha-synuclein are nodes in a complex pathogenetic nexus in dopaminergic neurons [20]. Whether MSA involves a similar pattern of catecholamine depletion, decreased vesicular sequestration, decreased ALDH activity, and DOPAL buildup has been unknown.

If such a pattern were observed in MSA, this would fit with the notion that a vesicular storage defect and ALDH inhibition are part of a common pathogenetic pathway in the death of central catecholamine neurons, independently of intra-neuronal alpha-synucleinopathy. It

could also lead to novel treatment and prevention strategies, based on reducing the production or decreasing the toxicity of catecholaldehydes [20].

To evaluate vesicular storage and ALDH activity in the putamen in MSA, we measured post-mortem tissue levels of catechols and catechol ratios. Essentially all of intra-neuronal DA is in vesicles, and DOPA is the immediate product of the rate-limiting tyrosine hydroxylation step in DA biosynthesis (Figure 1). The tissue DA:DOPA ratio therefore indicates DA storage for a given amount of DA production [12]. In tissues possessing noradrenergic terminal innervation, the ratio of 3,4-dihydroxyphenylglycol (DHPG, the main neuronal metabolite of norepinephrine) to norepinephrine (NE) provides another index of vesicular sequestration vs. oxidative deamination of cytoplasmic catecholamines [13]. The frontal cortex receives noradrenergic innervation derived from the locus ceruleus [21], and within the terminals NE is produced in vesicles after vesicular uptake of cytoplasmic DA. There is only sparse dopaminergic innervation from the substantia nigra [22]. The NE:DA ratio in frontal cortical tissue would then be expected to be decreased if there were a vesicular storage defect in the noradrenergic terminals [13]. Finally, the tissue ratio of DOPAC:DOPAL is a sensitive measure of ALDH activity [12].

In order to evaluate catecholamine metabolism in projection sites of the dopaminergic substantia nigra, we assayed the catechols in putamen and caudate, and to evaluate catecholamine metabolism in projection sites of the noradrenergic locus ceruleus, which are distributed widely in the brain, we assayed the catechols in frontal cortex, in a post-mortem neurochemical study.

MATERIALS AND METHODS

Patient Material

Post-mortem brain tissue was obtained from 15 patients with neuropathologically confirmed end-stage MSA, 17 idiopathic PD patients, and 18 control subjects, most of whom were autopsied at the University of Miami Brain Endowment Bank™. The study was conducted with approval of the Human Subjects Research Office (M809) of the University of Miami. Postmortem intervals (duration between death and brain freezing) were recorded and in all subjects were 24 hours. Lewy bodies and glial cytoplasmic inclusions were identified with antibodies to alpha-synuclein. The control subjects were selected to have similar mean age and postmortem intervals as the MSA and PD groups and were devoid of Alzheimer-related pathology.

Assays of Catechols in Tissue

The putamen samples were matched at the same posterior level and subregional localization. The samples were stored at -70 °C or colder until thawed for catechol assays in the Clinical Neurochemistry Laboratory at the NIH. The catechols in samples from MSA and control subjects were assayed in simultaneous runs. After obtaining the wet weight of the tissue, 500 µL per 100 mg tissue of a solution was added that contained 9.2 mL glacial acetic acid and 460 µL phosphoric acid per liter of water. The tissue was sonicated, and after centrifugation the supernate was frozen and stored at -70 °C or colder until assayed for catechols by liquid

chromatography with electrochemical detection after batch alumina extraction.[23] Briefly, mobile phase containing octanesulfonic acid as an ion pairing agent was pumped isocratically through a reverse phase liquid chromatographic column. Catechols were quantified by the current produced upon exposure of the eluate to a flow-through electrodes set to oxidizing and then reducing potentials in series, with recording from the last electrode reflecting reversibly oxidized species.

DOPAL standard was synthesized in the laboratory of and provided by Dr. Kenneth L. Kirk (NIDDK) or was obtained from Santa Cruz Pharmaceuticals (Santa Cruz, CA). Identity of the standard was confirmed by mass spectroscopy, nuclear magnetic resonance, and liquid chromatography with time-of-flight mass spectroscopy.

Data Analysis and Statistics

Tissue catechol concentrations were expressed as fmol/mg wet weight. For statistical tests individual neurochemical data were log transformed. This is a commonly used and appropriate approach when compared groups differ substantially not only in mean values but also in standard deviations and the standard deviations vary directly with the mean values.

Catechol concentrations in MSA or PD vs. control groups (in fmol per mg wet weight) were compared by independent means t-tests. Correlation coefficients relating neurochemical values across subjects were calculated by linear regression using Kaleidagraph 4.0 (Synergy Software).

RESULTS

Patient Demographics and Post-Mortem Intervals

In the MSA group, the mean age was 64.5 years (range 56-78 years), with 8 men and 7 women; 12 were Caucasian, 2 Hispanic, and 1 Greek. In the PD group, the mean age was 76.6 years (range 66-85 years), with 13 men and 4 women; all were Caucasian. In the control group, the mean age was 71.2 years (range 55-91 years), with 14 men and 4 women; 15 were Caucasian, 2 Hispanic, and 1 of mixed ethnic background. Mean post-mortem intervals (times from death until tissue freezing) were 11.0 hours in MSA, 8.9 hours in PD, and 13.6 hours in the controls.

Putamen

Compared to controls, putamen DA was decreased by 96% and DOPAC by 97% in MSA and by 93% and 95% in PD ($p < 0.0001$ each; Table 1, Figure 2A). As indicated by the gray box in the right panel in Figure 2A, all MSA patients had putamen DA and DOPAC levels below the control ranges. The scatter plot also shows that individual values for DOPAC and DA in the MSA and PD patients were about as predicted from the line of best fit in the controls.

In both MSA and PD, putamen concentrations of NE and DHPG were also decreased compared to controls (by 91% and 81% in MSA, $p < 0.0001$ each; by 74% and 74% in PD, $p < 0.0001$ each; Figure 2B). All MSA patients had putamen NE and DHPG levels below the control ranges. Among both MSA and PD patients, the DHPG concentration was greater

than expected for the NE concentration (all blue data points to the left of the manually placed line of best fit in the controls).

Among MSA and PD patients, NE concentrations were positively correlated with DA concentrations (Figure 3). For given DA concentrations, NE concentrations were higher than expected based on the control line of best fit.

Mean DOPAL was decreased in both MSA (by 94%) and PD (by 84%, $p<0.0001$ each). DOPAL:DA ratios were increased in both MSA (2.4 times control, $p=0.02$) and PD (3.5 times control, $p=0.009$).

Among MSA patients, 6 had putamen DOPA above the control range, presumably reflecting levodopa treatment prior to death. Excluding the data from these patients, mean DA:DOPA was decreased in both MSA and PD (by 94% and 88%, $p<0.0001$ each; Figure 4). Tissue DHPG:NE, an index of NE turnover, was increased in both MSA and PD (306% and 264% of control, $p=0.02$, $p=0.04$). In both the MSA and PD groups, the mean putamen DOPAC:DOPAL ratio was decreased from that in the control group (by 61% and 74%; $p=0.03$, $p=0.0007$). The MSA and PD groups did not differ in mean DOPAC:DOPAL ratios.

Caudate

Abnormalities of tissue catechols and catechol ratios in MSA and PD were generally less severe in the caudate than in the putamen. Caudate DA and DOPAC were decreased in MSA patients compared to control subjects (by 73% and 87%, $p<0.0001$ each). Tissue NE and DHPG were also decreased in both groups (by 80% and 72%; $p<0.0001$, $p=0.006$).

Caudate DOPA was above the control range in 1 MSA patient. Excluding the data from this patient, caudate DOPA was non-significantly decreased from the controls, in both the MSA and PD groups. DOPAL was non-significantly decreased in the MSA group but was significantly decreased in the PD group (by 57%, $p=0.002$). Mean DA:DOPA tended to be decreased in the MSA group (by 49%, $p=0.08$) and was significantly decreased in the PD group (by 72%, $p=0.0002$). In both MSA and PD, mean DHPG:NE in caudate was not different from that in the controls.

Frontal Cortex

In frontal cortex tissue, the MSA and PD groups had decreased NE content (by 81% and 50%; $p<0.0001$ each). The two groups did not differ in mean NE content. Both groups also had decreased DHPG content (by 70% and 57%; $p=0.0006$, $p=0.0002$). In the MSA and PD groups, mean frontal cortical contents of DA and DOPAC did not differ from those in controls. Cortical NE:DA ratios were markedly decreased in MSA (by 94% from control, $p<0.0001$) and PD (by 91% from control, $p<0.0001$).

Tissue DOPA

Putamen contents of DA, NE, DOPAC, and DHPG were not correlated with putamen DOPA content, a direct measure of levodopa/carbidopa treatment, whether considered across all subjects or considered only among the MSA patients.

DISCUSSION

We report here post-mortem tissue neurochemical evidence that MSA involves the same abnormal pattern of central catecholaminergic abnormalities as found in PD, including profound putamen DA depletion and decreased NE contents in both putamen and frontal cortex. In addition, the analogous abnormalities in catechol ratios in MSA and PD indicated similarly impaired vesicular storage and ALDH activity and accumulation of the autotoxic DA metabolite DOPAL. This pattern might reflect a final common pathway in the death of catecholamine neurons; if so, then the results have implications for treatment and prevention of both diseases, as explained below.

Several lines of evidence fit with a vesicular storage defect in catecholaminergic terminals in MSA. In the putamen, decreased DA:DOPA ratios indicated decreased DA storage for a given amount of synthesis [12], and increased DHPG:NE ratios indicated a shift from vesicular sequestration to oxidative deamination of cytoplasmic NE [13]. The frontal cortex receives noradrenergic innervation from the locus ceruleus and little if any dopaminergic innervation from the substantia nigra, and DA seems to be co-released with NE from noradrenergic terminals [22]. It is possible that DA in frontal cortex is localized to vesicles in noradrenergic terminals, and if so then low NE:DA ratios in MSA and PD would reflect decreased vesicular storage, since NE synthesis takes place in the vesicles after vesicular uptake of cytoplasmic DA [13].

Post-mortem evidence for a vesicular storage defect in central catecholaminergic terminals in both MSA and PD is consistent with our previous report of accelerated loss of putamen ^{18}F -DOPA-derived radioactivity in these diseases [24], because retention of ^{18}F -DOPA-derived radioactivity in the tissue depends on vesicular storage of the ^{18}F -DA produced from ^{18}F -DOPA in the cytoplasm. Conversely, we propose that accelerated loss of putamen ^{18}F -DOPA-derived radioactivity may be an *in vivo* biomarker of a vesicular storage defect.

There seems to be an association between a vesicular storage defect and loss of central catecholaminergic neurons in synucleinopathies. In the periphery, this association has been confirmed in PD [13]. In MSA there is little evidence for either abnormality in the periphery [14]. A potential explanation for similar neurochemical abnormalities in the brain and different neurochemical abnormalities in the periphery in MSA and PD is that MSA is primarily a disorder of glial cells (in particular, oligodendroglia), whereas PD is primarily a disorder of monoaminergic and cholinergic neurons. Since sympathetic post-ganglionic neurons in the heart are not myelinated and are maintained by nerve growth factor produced by target myocardial cells, oligodendroglial pathology would not be expected to lead to loss of the sympathetic neurons. On the other hand, in the brain, glial pathology in MSA could interfere with production or trafficking of glial cell line derived neurotrophic factors, which are absolutely required for survival of central catecholaminergic neurons [25].

The combination of depletion of vesicular DA stores and decreased ALDH activity explains drastically decreased tissue DOPAC in MSA and PD. Brain tissue DOPAC is correlated with CSF DOPAC [26]. The finding of low tissue DOPAC levels in both MSA and PD

provides post-mortem neurochemical validation of low CSF DOPAC levels as a biomarker of Parkinsonism [27-29].

As highlighted in Table 2, the neurochemical abnormalities found in putamen, caudate, and frontal cortex of MSA patients resembled those of PD patients. This similarity leads us to propose that decreased vesicular storage, decreased ALDH activity, and catecholaldehyde accumulation may be part of a common pathway in the death of catecholaminergic neurons. When there is no decrease in vesicular storage, as in the sympathetic nerves in MSA, there is no denervation, and when there is a decrease in vesicular storage, as in the sympathetic nerves in PD and in both MSA and PD in the putamen, there is denervation. Our results also question the concept that in PD intra-neuronal alpha-synucleinopathy is solely and directly responsible for the death of catecholaminergic neurons, as opposed to indirectly via interactions involving catecholamine oxidation products. Finally, the results suggest a novel experimental therapeutic hypothesis, that attenuating formation of catecholaldehydes or interfering with their toxic effects may slow the neurodegenerative loss of catecholamine neurons in both MSA and PD.

Study Limitations

The samples assayed in this study originated from several centers. Therefore, clinical data were few. Nevertheless, the format of the study ensured that group assignments were correct, because they were based on post-mortem neuropathologic findings.

In this study no data were obtained relevant to two key questions about the pathogenesis of MSA and PD. (1) Why is alpha-synuclein deposited in glial cells in MSA but in Lewy bodies in PD? and (2) Why is there a differential linkage of alpha-synucleinopathy with abnormal catecholamine metabolism in the brain and periphery these diseases? We hope the present results will help spur further efforts to answer these questions.

There was no information about the timing of levodopa dosing prior to death; however, after exclusion of data from patients with high putamen DOPA content, the key results of the study were unaffected.

Levels of 3,4-dihydroxyphenylethanol (DOPET) were below the detection limit in most MSA patients, so that meaningful statistical comparisons with PD patients and control subjects could not be done. As a result, we were not able to include DOPET:DOPAC ratios as an index of a shift from ALDH to aldehyde reductase, the alternative enzymatic pathway in DOPAL metabolism.

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The first author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations

ALDH	aldehyde dehydrogenase
DA	dopamine
DHPG	3,4-dihydroxyphenylglycol
DOPAC	3,4-dihydroxyphenylacetic acid
DOPAL	3,4-dihydroxyphenylacetaldehyde
MSA	multiple system atrophy
NE	norepinephrine
PD	Parkinson disease
VMAT	vesicular monoamine transporter

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Parkinson disease (PD) and multiple system atrophy (MSA) share some central neuropathologic findings but not others. In PD evidence has accrued for a vesicular storage defect and decreased aldehyde dehydrogenase activity in residual putamen terminals, resulting in buildup of the toxic dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL). In this study we found that MSA entails the same abnormal neurochemical pattern. The results fit with a common pathway in the death of catecholamine neurons in a variety of neurodegenerative diseases. Targeting this death pathway, by interfering with catecholaldehyde production or effects, constitutes a novel treatment approach.

Figure 1.

Diagrams of the synthesis and fate of dopamine (DA) and norepinephrine (NE). DA that leaks from vesicles (V) into the cytoplasm (C) or that is taken up via the cell membrane dopamine transporter (DAT) and escapes vesicular reuptake via the vesicular monoamine transporter (VMAT) is subject to oxidative deamination catalyzed by monoamine oxidase (MAO) to form the catecholaldehyde, dihydroxyphenylacetaldehyde (DOPAL). DOPAL is metabolized by aldehyde dehydrogenase (ALDH) to form dihydroxyphenylacetic acid (DOPAC), the major metabolic route, or aldehyde/aldose reductase (AR) to form dihydroxyphenylethanol (DOPET), the minor metabolic route. In contrast, the catecholaldehyde formed from NE, dihydroxyphenylglycolaldehyde (DOPEGAL), is detoxified mainly by AR to form dihydroxyphenylglycol (DHPG). Dihoxymandelic acid (DHMA) is a minor NE metabolite. Other abbreviations: NET=cell membrane norepinephrine transporter.

Figure 2.

Mean (± SEM) and individual values for putamen tissue concentrations of (A) DA and DOPAC and (B) NE and DHPG in patients with multiple system atrophy (blue), Parkinson disease (red), or control subjects (gray).

Figure 3. Scatter plot relating putamen tissue NE to DA in patients with multiple system atrophy (blue), Parkinson disease (red), or control subjects (gray).

Figure 4. Mean ($\pm$ SEM) values for putamen tissue concentration ratios of DA:DOPA, DHPG:NE, and DOPAC:DOPAL in patients with multiple system atrophy (blue), Parkinson disease (red), or control subjects (gray).

TABLE 1

Mean ($\pm$ SEM) values (fmol/mg wet weight) for putamen, caudate, and frontal cortex tissue contents of catechols in multiple system atrophy (MSA), Parkinson disease (PD), and control subjects (Control).

PUTAMEN				
Analyte	MSA	PD	Control	p MSA v Control
DA	555 $\pm$ 158	1003 $\pm$ 360	14446 $\pm$ 1770	<0.0001
DOPAC	100 $\pm$ 20	163 $\pm$ 56	3415 $\pm$ 537	<0.0001
DOPA	1081 $\pm$ 384 *	616 $\pm$ 120	1601 $\pm$ 468	n.s.
DOPAL	17 $\pm$ 5	86 $\pm$ 43	523 $\pm$ 154	<0.0001
NE	19 $\pm$ 4	54 $\pm$ 21	205 $\pm$ 28	<0.0001
EPI	3 $\pm$ 1	4 $\pm$ 3	107 $\pm$ 60	0.002
DHPG	3 $\pm$ 1	5 $\pm$ 1	17 $\pm$ 3	<0.0001

CAUDATE				
Analyte	MSA	PD	Control	p MSA v Control
DA	3110 $\pm$ 1130	2708 $\pm$ 724	11466 $\pm$ 1375	<0.0001
DOPAC	374 $\pm$ 162	376 $\pm$ 94	2842 $\pm$ 553	<0.0001
DOPA	805 $\pm$ 217 **	531 $\pm$ 80	1058 $\pm$ 288	n.s.
DOPAL	130 $\pm$ 70	166 $\pm$ 83	411 $\pm$ 83	n.s.
EPI	2 $\pm$ 1	4 $\pm$ 3	154 $\pm$ 119	0.001
NE	20 $\pm$ 7	39 $\pm$ 16	96 $\pm$ 20	<0.0001
DHPG	4 $\pm$ 1	6 $\pm$ 2	14 $\pm$ 4	0.006

CORTEX				
Analyte	MSA	PD	Control	p MSA v Control
DOPA	518 $\pm$ 222	352 $\pm$ 161	165 $\pm$ 16	n.s.
NE	8 $\pm$ 2	20 $\pm$ 13	40 $\pm$ 5	<0.0001
EPI	1.0 $\pm$ 0.3	1.6 $\pm$ 0.8	15 $\pm$ 5	<0.0001
DA	23 $\pm$ 12	18 $\pm$ 6	13 $\pm$ 5	n.s.
DHPG	2 $\pm$ 1	3 $\pm$ 1	8 $\pm$ 2	0.0006
DOPAL	1 $\pm$ 1	9 $\pm$ 3	7 $\pm$ 2	n.s.
DOPAC	13 $\pm$ 7	6 $\pm$ 2	6 $\pm$ 1	n.s.

Notes:

Values below the minimum detectable level were assigned a value of zero. Values for p based on independent-means t-tests conducted on log-transformed data. The MSA and PD groups did not differ significantly for any of the analytes.

* Data for 6 patients not counted (above the maximum detectable level).

** Data for 1 patient not counted (above the maximum detectable level).

TABLE 2

Summary of abnormalities in MSA and PD compared to controls.

Parameter	MSA	PD
<i>Putamen</i>		
DOPA	Not different	Low
DA	Very Low	Very Low
DOPAL	Low	Low
NE	Low	Low
DHPG	Low	Low
DA:DOPA	Low	Low
DOPAC:DOPAL	Low	Low
NE:DA	High	High
DHPG:NE	High	High
<i>Caudate</i>		
DOPA	Not different	Low
DA	Low	Low
DOPAL	Not different	Low
NE	Low	Low
DHPG	Low	Low
DA:DOPA	Not different	Low
DOPAC:DOPAL	Not different	Low
NE:DA	Not different	Low
DHPG:NE	Not different	Not different
<i>Cortex</i>		
DOPA	Not different	Not different
DA	Not different	Not different
DOPAL	Not different	Not different
NE	Low	Low
DHPG	Low	Low
DA:DOPA	Not different	Not different
DOPAC:DOPAL	Not different	Not different
NE:DA	Low	Low
DHPG:NE	Not different	Low