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Short communication

Determinants of denervation-independent depletion of putamen dopamine in Parkinson's disease and multiple system atrophy

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ABSTRACT

Background: Severe putamen dopamine depletion characterizes Parkinson's disease (PD) and multiple system atrophy (MSA). The extent of the depletion is greater than can be accounted for by loss of nigrostriatal dopaminergic terminals alone. We used putamen tissue levels and ratios of cysteinyl and parent catechols to explore possible denervation-independent abnormalities of dopamine synthesis and fate in PD and MSA. 5-S-Cysteinyldopa (Cys-DOPA) is produced from spontaneous oxidation of DOPA and 5-S-cysteinyldopamine (Cys-DA) from spontaneous oxidation of DA.

Methods: Post-mortem putamen tissue samples from 17 PD and 25 MSA patients and 30 controls were assayed for endogenous catechols including DA, its cytoplasmic metabolites (Cys-DA, 3,4-dihydroxyphenylacetic acid, 3,4-dihydroxyphenylethanol, and 3,4-dihydroxyphenylacetaldehyde), and tyrosine hydroxylation products proximal to DA (DOPA and Cys-DOPA).

Results: The PD and MSA groups did not differ in mean values of parent or cysteinyl catechols, and the data for the two groups were lumped. In the patients an index of vesicular storage of DA (the ratio of DA to the sum of its cytoplasmic metabolites) averaged 54% of control ($p = 0.001$), and an index of L-aromatic-amino-acid decarboxylase (LAAAD) activity (the ratio of DA and the sum of its cytoplasmic metabolites to the sum of DOPA + Cys-DOPA) averaged 21% of control ($p < 0.0001$). An index of innervation (the sum of DOPA + Cys-DOPA) averaged 63% of control ($p = 0.01$).

Interpretation: Based on patterns of parent and cysteinyl catechols in putamen, PD and MSA involve decreased vesicular uptake and decreased LAAAD activity in the residual dopaminergic terminals. The combination seems to contribute importantly to dopamine depletion in these diseases.

The parkinsonian movement disorder in Parkinson's disease (PD) and multiple system atrophy (MSA) is associated with profound depletion of the catecholamine, dopamine (DA), in the putamen [1]. It is widely presumed that this deficiency directly and solely reflects loss of nigrostriatal neurons; however, the extent of putamen DA depletion in PD (more than 90% in most studies) is greater than can be accounted for by the loss of nigral dopaminergic neurons or striatal dopaminergic terminals alone (about 60–80%) [2,3].

The difference could reflect denervation-independent abnormalities of DA storage and synthesis in the residual neurons. Recent studies have supported the view that both PD and MSA involve a decreased ability to retain catecholamines in vesicles [4,5], and essentially all of putamen DA content is in the vesicles. In addition, PD is associated with decreased activity of L-aromatic-amino-acid decarboxylase (LAAAD) [6]. Since LAAAD is required for DA synthesis from DOPA, LAAAD deficiency could also contribute to DA depletion.

We used simultaneous measurements of parent and cysteinyl catechols to examine these possibilities. Inspection of the concept diagram in Fig. 1 helps understand the indices chosen to assess

Abbreviations: ALDH, aldehyde dehydrogenase; DA, dopamine; DHPG, 3,4-dihydroxyphenylglycol; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOPET, 3,4-dihydroxyphenylethanol; MSA, Multiple system atrophy; NE, norepinephrine; PD, Parkinson's disease; VMAT, vesicular monoamine transporter.

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vesicular storage, LAAAD activity, and denervation. DOPA is decarboxylated enzymatically to form DA, and DA is deaminated enzymatically to form the intermediate metabolite 3,4-dihydroxyphanylacetaldehyde (DOPAL), followed by enzymatic conversion to 3,4-dihydroxyphenylacetic acid (DOPAC) or to the minor metabolite 3,4-dihydroxyphenylethanol (DOPET). A small proportion of cytoplasmic DOPA undergoes spontaneous oxidation to form DOPA-quinone and then 5-S-cysteinyl-DOPA (Cys-DOPA); and a small proportion of cytoplasmic DA undergoes spontaneous oxidation to form 5-S-cysteinyl-dopamine (Cys-DA). Cys-DOPA is not a substrate for LAAAD [7].

From inspection of Fig. 1, if there were vesicular storage defect, then the ratio of DA, in green, to the sum of its cytoplasmic metabolites (i.e., DA/(DOPAC + Cys-DA + DOPAL + DOPET)), in pink, would be decreased. If there were attenuated LAAAD activity, then the ratio of DA and its metabolites, in pink and green, to the sum of the tyrosine hydroxylase products proximal to DA (i.e., DOPA + Cys-DOPA), in aqua, would be decreased. Finally, if there were denervation, then the local concentration of TH activity would be expected to be decreased, and so the sum of DOPA + Cys-DOPA, in aqua, which are two products of TH acting on tyrosine proximal to the LAAAD step, would be decreased.

1. Methods

1.1. Patient material

Post-mortem brain tissue was obtained from 17 patients with neuropathologically confirmed sporadic PD, 21 patients with MSA, and 25 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. Post-mortem intervals (duration between death and brain freezing) were recorded and in all subjects were ≤24 h. Lewy bodies and glial cytoplasmic inclusions were identified with antibodies to alpha-synuclein. The control subjects were selected to have similar mean age and post-mortem intervals as the PD and MSA groups and did not have Alzheimer-related pathology.

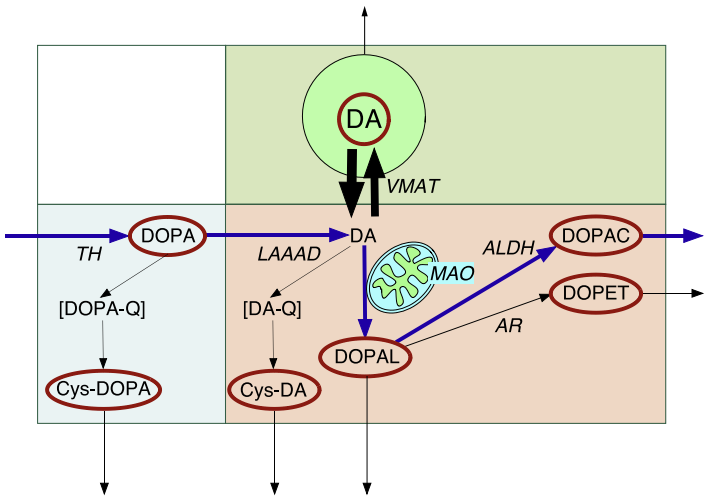
1.2. Assays of catechols in tissue

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 our laboratory [8].

1.3. 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.

Most of the samples had been assayed previously, before we had developed methodology for simultaneous measurements of



Decreased vesicular sequestration (decreased VMAT activity):

Decreased DA / (DOPAC+Cys-DA+DOPAL+DOPET)

Decreased LAAAD activity:

Decreased (DA+DOPAC+Cys-DA+DOPAL+DOPET) / (DOPA+Cys-DOPA)

Decreased innervation (decreased TH activity):

Decreased DOPA + Cys-DOPA

Fig. 1:. Concept diagram about sources and metabolic fate of dopamine in putamen tissue. Tyrosine hydroxylase (TH) catalyzes the conversion of tyrosine to DOPA, and L-aromatic-amino-acid decarboxylase (LAAAD) converts DOPA to dopamine (DA). Most of the DA in putamen tissue is in vesicles, due to uptake mediated by the vesicular monoamine transporter (VMAT). Cytoplasmic DA can be metabolized by monoamine oxidase (MAO) in the outer mitochondrial membrane to form 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is metabolize by aldehyde dehydrogenase (ALDH) to form 3,4-dihydroxyphenylacetic acid (DOPAC) or by aldehyde/aldose reductase (AR) to form 3,4-dihydroxyphenylethanol (DOPET). Cytoplasmic DA can oxidize spontaneously to form DA-quinone (DA-Q) and then 5-S-cysteinyl-DA (Cys-DA), and cytoplasmic DOPA can oxidize spontaneously to form DOPA-quinone (DOPA-Q) and then 5-S-cysteinyl-DOPA (Cys-DOPA). The rectangle in aqua corresponds to products of TH proximal to DA; in pink to cytoplasmic DA metabolites; and in green to vesicular DA.

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