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Catecholamine autotoxicity. Implications for pharmacology and therapeutics of Parkinson disease and related disorders ☆

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ABSTRACT

Several neurodegenerative diseases involve loss of catecholamine neurons—Parkinson disease is a prototypical example. Catecholamine neurons are rare in the nervous system, and why they are vulnerable in PD and related disorders has been mysterious. Accumulating evidence supports the concept of "autotoxicity"—inherent cytotoxicity of catecholamines and their metabolites in the cells in which they are produced. According to the "catecholaldehyde hypothesis" for the pathogenesis of Parkinson disease, long-term increased build-up of 3,4-dihydroxyphenylacetaldehyde (DOPAL), the catecholaldehyde metabolite of dopamine, causes or contributes to the eventual death of dopaminergic neurons. Lewy bodies, a neuropathologic hallmark of PD, contain precipitated alpha-synuclein. Bases for the tendency of alpha-synuclein to precipitate in the cytoplasm of catecholaminergic neurons have also been mysterious. Since DOPAL potently oligomerizes and aggregates alpha-synuclein, the catecholaldehyde hypothesis provides a link between alpha-synucleinopathy and catecholamine neuron loss in Lewy body diseases. The concept developed here is that DOPAL and alpha-synuclein are nodes in a complex nexus of interacting homeostatic systems. Dysfunctions of several processes, including decreased vesicular sequestration of cytoplasmic catecholamines, decreased aldehyde dehydrogenase activity, and oligomerization of alpha-synuclein, lead to conversion from the stability afforded by negative feedback regulation to the instability, degeneration, and system failure caused by induction of positive feedback loops. These dysfunctions result from diverse combinations of genetic predispositions, environmental exposures, stress, and time. The notion of catecholamine autotoxicity has several implications for treatment, disease modification, and prevention. Conversely, disease modification clinical trials would provide key tests of the catecholaldehyde hypothesis.

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Abbreviations: ALDH, aldehyde dehydrogenase; AR, aldehyde reductase; BRA, baroreflex area; CSF, cerebrospinal fluid; DA, dopamine; DHPG, 3,4-dihydroxyphenylglycol; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAL, 3,4-dihydroxyphenylacetaldehyde; 3,4-DOPEGAL, dihydroxyphenylglycolaldehyde; EPI, epinephrine; 4-HNE, 4-hydroxynonenal; MAO, monoamine oxidase; LBD, Lewy body dementia; MSA, multiple system atrophy; NE, norepinephrine; OH, orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson disease; PET, positron emission tomography; REM, rapid eye movement; SAS, sympathetic adrenergic system; SNS, sympathetic noradrenergic system; TH, tyrosine hydroxylase; VMAT, vesicular monoamine transporter.

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1. Introduction

The burden of diseases of senescence is increasing as the population ages. Neurodegenerative diseases pose major challenges both to public health and medical science. In general, symptoms of these diseases are treatable, but the treatments do not reverse the neurodegeneration. Theoretically, disease progression might be retarded if the pathogenetic process were detected early and effective disease-modifying treatment instituted in a pre-symptomatic phase.

Parkinson disease (PD) was the first neurodegenerative disease for which the underlying neurochemical abnormality was identified—severe depletion of the catecholamine dopamine (DA) in the striatum (Ehringer & Hornykiewicz, 1960). Alleviation of the deficiency by levodopa treatment was revolutionary in the history of medical neuroscience (Cotzias, 1971). All current approved treatments of PD work directly or indirectly by countering effects of striatal DA depletion. While often effective in alleviating symptoms, no PD treatment has been proven to slow the loss of nigrostriatal neurons.

Almost a century ago, in his thesis published in 1919, Constantin Tretiakoff described for the first time two of what are now considered to be characteristic neuropathologic features of PD—a loss of pigmentation in the substantia nigra in the midbrain and nigral "corps de Lewy" (Lewy bodies). The latter designation was in recognition of the description 6 years previously, by Friedrich Lewy, of intra-neuronal hyaline inclusions in patients with paralysis agitans.

Substantia nigra depigmentation likely has a neurochemical basis—loss of neurons that contain DA, since DA auto-oxidizes spontaneously to form melanin (from the Greek word for black). Tretiakoff's discoveries about nigral depigmentation and Lewy bodies in substantia nigra neurons in PD, and subsequent findings showing that putamen DA is severely depleted in PD (Kish et al., 1988; Wilson et al., 1996; Hornykiewicz, 1998) and that Lewy bodies contain abundant precipitated alpha-synuclein (Spillantini et al., 1997; Mezey et al., 1998) lead to two sets of questions, which to a major extent inspired this review.

First, catecholamine neurons are rare in the nervous system. Why are they lost in PD? What makes them different from neurons of other transmitter types? What renders catecholamine neurons, including nigral dopaminergic neurons and striatal dopaminergic terminals, susceptible?

Second, Lewy bodies contain abundant aggregated alpha-synuclein, and at least in rare forms of familial PD abnormalities of the alpha-synuclein gene are etiologic (Polymeropoulos et al., 1997; Singleton et al., 2003). Why does alpha-synuclein tend to precipitate in catecholaminergic neurons in PD?

The title of this review is a proposed answer to the first set of questions. The thesis developed here is that the unusual vulnerability of catecholamine neurons is related to inherent cytotoxicity of catecholamines and their metabolites in the cells in which they are produced—"catecholamine autotoxicity." Catecholamines spontaneously oxidize to form quinones, chromes, polydopamine, condensation products (e.g., salsolinol), melanin, and neuromelanin. Catecholamines are also subject to enzymatic oxidation mediated by monoamine oxidase (MAO), with the immediate products being hydrogen peroxide and aldehydes. As discussed in detail in this review, there are numerous potential pathogenetic links between the aldehydes and alpha-synuclein. One of them, aldehyde-induced oligomerization of alpha-synuclein, may help explain alpha-synuclein precipitation in Lewy bodies within monoaminergic neurons in PD.

2. Overview of the autotoxicity concept

In this review much attention will be given to the "catecholaldehyde hypothesis" (Panneton et al., 2010; Goldstein, Holmes et al., 2011; Goldstein, Sullivan et al., 2011; Goldstein, Sullivan et al., 2012; 2013). Briefly, the preponderance of intra-neuronal metabolism of endogenous DA occurs via formation of the catecholaldehyde, 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is toxic. In general, the toxicity occurs by two routes—peroxidation of lipid membranes due to generation of reactive oxygen species and inactivation of enzymes and transporters due to protein cross-linking (Fig. 1).

As explained below in detail, we do not mean to imply here that DOPAL is the cause of PD or of any other neurodegenerative disease. Rather, according to the catecholaldehyde hypothesis, DOPAL is a node in a complex network of interacting homeostatic systems. Dysfunctions of several processes—including decreased vesicular sequestration of cytoplasmic DA and decreased DOPAL metabolism by aldehyde dehydrogenase (ALDH)—result from diverse combinations of genetic predispositions, environmental exposures, stress, and time. These abnormalities lead to conversion from the stability afforded by negative feedback regulation to the instability, degeneration, and system failure caused by induction of positive feedback loops (Goldstein, 2013).