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EDITORIAL

Elevated norepinephrine may interact with alpha-synuclein to promote Parkinson's disease and DLB

The pathophysiology underlying Parkinson's disease (PD), as well as dementia with Lewy bodies (DLB), is beginning to be elucidated. It has already been documented that the locus coeruleus, a brainstem nucleus that provides noradrenergic input to widespread regions of the brain, degenerates at an early timepoint in both PD and DLB, and this putative loss of noradrenergic signaling appears to have deleterious consequences in both disorders. A number of studies also have shown that norepinephrine (NE) interacts with alpha-synuclein, a protein that is a principal component of Lewy bodies, which are histopathological structures that are typically present inside large numbers of neurons in individuals suffering from PD or DLB. This Editorial very briefly explores the hypothesis that *elevated* NE, which has previously been suggested to be an etiological factor in some cases of PD and related forms of dementia,[1,2] interacts with alpha-synuclein before and during disease progression to modulate some cases of PD and DLB.

A number of studies have demonstrated that NE may modulate both the formation and the stabilization of alpha-synuclein inclusions. Chronic administration of the NE boosting antidepressant desipramine to Wistar-Kyoto rats increases production of alpha-synuclein in frontal cortex, hippocampus, and amygdala.[3] It has also been suggested that catecholamines such as NE can cause alpha-synuclein to aggregate and form Lewy bodies in the course of PD. Others have shown that NE can inhibit the formation and aggregation of insoluble alpha-synuclein fibrils, resulting in a more toxic oligomeric form of alpha-synuclein.

Alpha-synuclein, in turn, has also been demonstrated to modulate noradrenergic signaling, including its compartmentalization within brain regions. Several studies have shown, for example, that alpha-synuclein regulates signaling through the NE transporter (NET) or storage of NE in presynaptic vesicles. When alpha-synuclein is expressed at low levels, it can promote greater presynaptic NET activity and trafficking to the cell surface, whereas higher levels of alpha-synuclein expression can do the opposite.[4] Higher levels of functional NET at the cell surface would be expected to reduce noradrenergic signaling, whereas lower levels should increase synaptic signaling. *In vitro* data have also suggested that alpha-synuclein can interfere with upregulation of dopamine beta-hydroxylase, the enzyme that converts dopamine to NE.[5]

The studies described above suggest that there are a number of interactions between noradrenergic signaling and alpha-synuclein. One interpretation of these data is that NE facilitates production and aggregation of alpha-synuclein as a negative feedback mechanism to counteract elevated noradrenergic signaling. This interpretation is consistent with the data on desipramine enhancing production of alpha-synuclein,[3] where low levels of this protein enhance NET activity at the cell surface to decrease noradrenergic transmission (whereas high levels paradoxically may increase transmission).[4] This compensatory hypothesis is also consistent with the data on alpha-synuclein blocking upregulation of dopamine beta-hydroxylase.[5] In a prior publication, I have suggested that elevated noradrenergic signaling, especially its sustained elevated tone, is an etiological factor in some cases of PD.[2] Three more recent publications have asserted that while there is degeneration of the locus coeruleus at an early stage in PD and Alzheimer's disease, there may be compensatory mechanisms in the remaining locus coeruleus neurons that, however, prevent diminished noradrenergic signaling, especially at an early stage in these diseases.[6–8] Other studies have suggested that such noradrenergic compensatory mechanisms in response to locus coeruleus degeneration may exist in DLB and Alzheimer's disease, but perhaps to a lesser degree in PD. One possibility is that locus coeruleus degeneration is itself a compensatory mechanism for counteracting long-term elevated noradrenergic signaling in PD and DLB.

Since signaling in the sympathetic nervous system is known to ramp upward during aging, it is plausible that *elevated* noradrenergic signaling, rather than deficits, may be associated with the emergence of various diseases such as PD and DLB late in life.[9] It is suggested here that in *most* cases of PD or DLB, long-term elevated NE drives disease progression throughout the course of the disease, partially through its modulation of alpha-synuclein production and aggregation. In this scenario, noradrenergic transmission reducing pharmacological agents (such as clonidine, guanfacine, dexmedetomidine, propranolol, carvedilol, nebivolol, prazosin, and terazosin) may help prevent or treat existing cases of PD or DLB, where some therapeutic data already exist for terazosin.[10] A recent study has demonstrated that dexmedetomidine counteracts dopaminergic cell death in the substantia nigra pars compacta, in a mouse model of PD. There may, however, be a less common subgroup of individuals with either of these two diseases, who have *reduced* NE both prior to and during disease progression. Such individuals may benefit from noradrenergic transmission enhancing drugs such as desipramine, nortriptyline, reboxetine, atomoxetine, or isoproterenol.

KEYWORDS

clonidine, dementia, guanfacine, locus coeruleus, neurodegenerative disorders, noradrenaline, propranolol, tricyclic antidepressants

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Paul J. Fitzgerald

Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

Correspondence

Paul J. Fitzgerald, Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA.
Email: pfitz1940@gmail.com

ORCID

Paul J. Fitzgerald https://orcid.org/0000-0002-5216-2189

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