Proteasome Function and Pathological Proteins in the Pathogenesis of Parkinson’s Disease

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Parkinson’s disease (PD) is a multifactorial disease that appears to arise from the effects of both genetic and environmental influences (1). Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) showed rigidity, akinesia, stooped posture, and response to levodopa therapy; and it was indistinguishable from idiopathic PD. The discovery of MPTP demonstrated that toxic substances could cause PD. Epidemiological studies showed that pesticides and heavy metals are the principle environmental factors that appear to have an impact on the development of PD. The genetic contribution in PD has been debated for over a century. More recently, an increasing number of well-documented multigenerational parkinsonian kindreds have been reported with evidence of autosomal dominant inheritance with variable penetrance. Genes associated with either PD or Parkinson-related disorders include parkin, DJ-1, ubiquitin C-terminal hydrolase isozyme L1 (UCH-L1), nuclear receptor-related factor 1, and α-synuclein. α-Synuclein is particularly notable because it aggregates and is the main component of Lewy bodies (LBs). Because ubiquitin also accumulates in LBs, and parkin and UCH-L1 interact with the ubiquitin proteasomal system, proteasomal dysfunction is thought to contribute to the pathophysiology of PD. However, α-synuclein expression levels by themselves have no significant effect on proteasome peptidase activity, subunit expression, and proteasome complex assembly and function (2). Other mechanisms resulting in synuclein aggregation (not simply expression levels) may be the key to understanding the possible effect of aggregated synuclein on proteasome function. Aggregated α-synuclein binds to the proteasome and inhibits proteasomal activity. When rats were treated with stereotoxic unilateral infusion of lactacystin, a selective proteasome inhibitor, into the substantia nigra pars compacta, the animals became progressively bradykinetic, adopted a stooped posture, and displayed contralateral head tilting. Administration of apomorphine to lactacystin-treated rats reversed behavioral abnormalities and induced contralateral rotations (3). Lactacystin caused dose-dependent degeneration of dopaminergic cell bodies and processes with the cytoplasmic accumulation and aggregation of α-synuclein to form inclusion bodies. When proteasome inhibitors were injected systematically into adult rats over a period of 2 weeks, animals developed progressive parkinsonism with bradykinesia, rigidity, tremor, and an abnormal posture, which improved with apomorphine treatment. These findings support the notion that failure of the ubiquitin-proteasome system to degrade and clear unwanted proteins is an important etiopathogenic factor in PD (4).

On the other hand, Inden et al. found that injection of proteasome inhibitors to the substantia nigra pars compacta of rats did not cause cell loss or dysfunction of dopaminergic cells and protected dopaminergic cells from the toxic effect of 6-hydroxydopamine (6-OHDA) (5). These results showed the proteasome-involved toxic effect of 6-OHDA and inhibition of the proteasome in the animals subjected to 6-OHDA treatment caused inclusion bodies that did not cause cell loss. Accumulation of α-synuclein might protect the dopaminergic cells from the 6-OHDA toxicity as aggresomes. Parkin protein functions as a ubiquitin ligase. Mutations in the parkin gene induce ubiquitin-proteasome dysfunction and cause autosomal recessive juvenile parkinsonism. However, most patients with park2 PD did not exhibit the LBs.

The dose of proteasome inhibitors or the state of proteasome inhibited might cause the different results in...
these reports. More studies would be needed to reveal the function of the proteasome in the neurodegeneration of dopaminergic cells.

References

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