

Neurotrophic Hormone Deficiency Theory

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1 Overview

Neurotrophic Hormone Deficiency Theory was originally proposed by Appel et al., (1981) and is a modification to the Accelerated Aging Theory. This theory suggests that accelerated aging to particular neural areas is due to the presence of certain extrinsic factors¹. The areas with these extrinsic factors experiencing accelerated aging (Degeneration) and are the common underlying cause of [ALS](#), Parkinsonism, and Alzheimer's Disease.

2 Commonalities of ALS, PD, and AD

To understand this theory, one must first understand the overlapping concepts of each of these diseases.

- All 3 diseases have changes in presynaptic neuronal input with secondary alterations of the target tissue¹
- All 3 diseases sporadically occur later in life and the incidence increases with age¹
- All 3 diseases have a familial form that occurs in 5-10% of patients¹
- Heavy metal intoxication is a secondary cause of these diseases¹

2.1 Presynaptic neuron changes + Target tissue alterations

- [ALS](#) has changes in Betz cells, CN motor neurons, and anterior horn cells¹
- PD includes changes in Substantia nigra neurons¹
- Alzheimer's disease includes changes in the cholinergic input from nucleus basalis and septal neurons to cortex and hippocampus¹

2.2 Secondary Heavy Metal Onset

- ALS: Lead¹
- PD: Manganese¹
- Alzheimer's Disease: Aluminum (evidence is weak)¹

3 Accelerated Aging Theory

The Neurotrophic Hormone Deficiency Theory adds onto the accelerated aging theory. The accelerated aging theory refers to the idea that the relevant neural areas are experiencing accelerated aging, and therefore and degenerating faster¹.

3.1 Advantages of the theory

1. This theory explains why external causes such as viral nor abnormal factors have yet to be discovered for these 3 diseases.
2. This theory helps to explain why there is a prevailing and consistent genetic incidence of ALS, PD, AD¹
3. Accelerated aging explains why disease incidence worsens with age¹

4. Lastly, this theory explains why external toxic factors such as heavy metal toxicity, trauma, viruses, infections, and vascular disease may increase the progression of these diseases

3.2 Disadvantages

- It should be noted that this theory does not provide specific insight as to the selective vulnerability of these neuronal networks¹.
- This theory does not offer meaningful and potentially useful therapeutic approaches to ALS, PD, or dementia/AD¹.

4 Mechanism

Neurotrophic Hormone Deficiency Theory adds to the accelerated aging idea by suggesting that the areas that undergo accelerated aging is based on intrinsic neuronal properties¹. Specifically, this theory hypothesizes that each disease (ALS, PD, AD), experiences degeneration due to diminished availability of a specific neurotrophic hormone¹. This neurotrophic hormone is normally released by the postsynaptic cell, taken up by the presynaptic terminal, and exerting its effect by retrograde transport up the presynaptic axon to the soma and nucleus¹.

4.1 Practical examples of this theory

4.1.1 ALS

In ALS, if the muscle cells fail to release appropriate or enough motor neurotrophic hormones then there will be a failure in the anterior horn cells¹. Gradually, this will result in a gradual cessation of anterior horn cell function, resulting in cell death¹. In the upper motor neurons, Betz cells would result from diminished release of neurotrophic hormone from the target neurons¹. The target neurons of Betz cells cannot be defined further due to lack of knowledge on the subject¹.

4.1.2 PD

- Striatal cells are unable to provide the requisite dopamine (neurotrophic hormone)¹

4.1.3 Alzheimer's Disease

- Hippocampus and cortical cells fail to supply the cholinergic neurotrophic hormone¹

5 Implications

If certain neural structures are degrading due to lack of a requisite neurotrophic hormone then restoring hormone levels may restore the failing presynaptic cells¹.

1. Appel SH. A unifying hypothesis for the cause of amyotrophic lateral sclerosis, parkinsonism, and Alzheimer disease. *Annals of Neurology*. 1981;10(6):499-505. doi:[10.1002/ana.410100602](https://doi.org/10.1002/ana.410100602)