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Amino
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# *Chapter II*

## Novel roles of amino acids and analogues in neurodegenerative disorders – Introduction

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Amino acids have been historically viewed as relatively benign biological substances, considered largely to be the essential precursors for amino acids, peptides, or neurotransmitters. Our perspective on amino acids began to change, following John W. Olney's landmark discovery of neurotoxic properties of glutamate and other excitatory amino acids. Ten years earlier, around 1960, Oleh Hornykiewicz conducted a series of studies which spurred the testing and subsequent development of levodopa (L-DOPA) as a treatment of Parkinson's disease (PD). Forty years later, L-DOPA is still the most efficacious drug for treating PD. These two developments changed our perspective on amino acids.

Since 1970, amino acids have been increasingly viewed as multifactorial biological entities. In the field of Neuroscience, major efforts have been devoted to enhancing amino acid neuro-/ excito-toxicity, uncovering their mechanisms of toxicity, and probing ways to neuroprotect from amino acid toxicity. As more was learned amino acids took the position of both neurotoxic and neuroprotective, according to cellular health status and intracellular millieu.

In this particular chapter, some of the background (above) is explained in greater detail, providing insight into the newest developments on amino acids as neurotoxicants and neuroprotectants. And the practicality of such experimental findings is highlighted by papers on novel approaches towards the development of totally new classes of drugs for treating Parkinson's disease and other neurodegenerative disorders, by blocking glutamate receptor or by targeting production of abnormal proteins in neurodegenerative diseases.

Professor Oleh Hornykiewicz' review takes us from the synthesis of D,L-DOPA in 1911, into the occasional biological studies with DOPA prior to 1960, and through H. Blaschko and P. Holtz' correctly deduced role of L-DOPA as precursor in dopamine-, norepinephrine-, and epinephrine-synthesis. As described, dopamine was found to be present in brain, largely concentrated in corpus striatum (basal ganglia), able to be depleted by reserpine and replenished by DOPA. It was he, however, who had the foresight to explore the potential for L-DOPA as a useful antiparkinsonian drug. In 1960, Hornykiewicz and H. Ehringer autopsied Parkinsonian and non-Parkinsonian human brains and determined that dopamine was largely depleted in the brain of Parkinsonians. Hornykiewicz, with W. Birkmayer, then conducted the definitive study, treating Parkinsonians with DOPA. This clinical "trial" proved L-DOPA's usefulness in reversing the motor syndromes of bradykinesia and tremor, and reversing the motor "paralysis" in human Parkinsonians. Eventually, G. C. Cotzias and his group instituted high-dose L-DOPA, now the common treatment for PD. This remarkably important discovery changed the face of amino acids, from inert substance to useful drug. As Hornykiewicz concludes in his paper, L-DOPA is still changing its face, now perhaps as a neurotransmitter in its own right.

Dr. Diana Metodiewa, A. Kochman and C. Koka take Prof. Hornykiewicz' findings one step further – actually one metabolic step earlier in the dopamine synthetic schema: Tyr $\rightarrow$ L-DOPA $\rightarrow$ Dopamine – and explore the role of tyrosine (Tyr) as an endogenous principle in regulating cellular processes. Focus is on the potential for tyrosyl radical (TyrO$^{\bullet}$), protein

peroxides [(TyrOOH), o,o′-dityrosine (DT)] and 3-nitrotyrosine (3-NT) to form from reactive oxygen species (ROS) and reactive nitrogen species (RNS) when neurons are under oxidative stress. As reported, all such tyrosyl species are increased when (dopaminergic) nerves are damaged. TyrO$^{\bullet}$, being a free radical, initiates chain propagating reactions, while the other indicated tyrosyl species are highly reactive and able to 1) produce intraneuronal damage through lipid peroxidation, protein degradation, uncoupling of oxidative phosphorylation [or block of mitochondrial cytochromes], and thus 2) alter signal transduction, 3) lead to dopamine synthesis-failure, 4) contribute to proteopathic protein deposits (e.g., Lewy bodies), and 5) induce apoptosis. Thus, the role of Tyr is greatly expanded, from its being simple precursor in dopamine synthesis, to Tyr's broader role as intracellular neurotoxic species that might promote and accelerate the development and progression of neurodegenerative disorders, including PD.

In a similar vein, R. M. Kostrzewa, J. P. Kostrzewa, and R. Brus explore the neurotoxic and neuroprotective potential of L-DOPA. Both L-DOPA and dopamine, being catechols, autoxidize to quinones and semiquinones, themselves being ROS that tend to react similarly to that described for TyrO$^{\bullet}$. In addition, during the course of dopamine metabolism by monoamine oxidase (MAO), one molecule of hydrogen peroxide ($H_2O_2$) is generated for every molecule of dopamine. Although $H_2O_2$ is not particulary toxic, and is degraded by intraneuronal catalase, $H_2O_2$ does cross lipid membranes and generates more cytotoxic ROS such as superoxide ($O_2^{-\bullet}$) and hydroxyl radical (HO$^{\bullet}$), as well as nitrated species such as $^{\bullet}NO_2$, and $^{\bullet}$NO. In vitro, L-DOPA promotes apoptosis in virtually any cell, neuronal or non-neuronal. There is abundant evidence of oxidative stress in the substantia nigra and caudate of post-mortem brain of Parkinsonians. Conversely, in some studies L-DOPA sequesters ROS and inactivates HO$^{\bullet}$, thus serving a neuroprotectant function. It is this double nature of L-DOPA that uniquely positions L-DOPA with both neurotoxic and neuroprotective properties.

In the study by T. Archer, T. Palomo and A. Fredriksson, several classes of N-methyl-D-aspartate (NMDA) receptor antagonists were shown to increase locomotor activity in MPTP-treated mice that had been rendered tolerant to L-DOPA's antiparkinsonian effect. Beneficial effects were seen with the noncompetitive NMDA blockers memantine, amantadine, and MK-801, as well as with the competitive NMDA blocker CGP 40116 and the anticonvulsants lamotrigine and FCE 26743. Although amantadine, a noncompetitive NMDA receptor antagonist is useful alone in treating human PD, it is thought that the real potential of NMDA blockers lies in their ability to prevent the "wearing-off" of L-DOPA efficacy.

The study by L. C. Walker, F. Bian, M. J. Callahan, W. J. Lipinski, R. A. Durham and H. LeVine proposes yet another approach toward the treatment of neurodegenerative disorders, namely in directing treatment towards metabolic processes involved in synthesis and aggregation of protein polymers (i.e., proteopathies) that typify these disorders. Representative examples include the Lewy bodies in PD and A$\beta$-aggregates of senile plaques in Alzheimer's disease (AD) as well as the neurofibrillary tangles in AD. Although it is not know if these protein aggregates are 1) a byproduct of the neurodegenerative disorder or 2) a causative principle, it is known that these protein aggregates worsen the condition. By taking an extract of AD brain and infusing it intracerebrally in Tg2576 mice at 3 months of age, the following effects occurred: premature deposition of $\beta$-amyloid, augmented amyloid load, increased pathology, and tau hyperphosphorylation in axons traversing a lesion site. It is expected that this new animal model will be an ideal means for exploring mechanisms underlying abnormal protein aggregates in neurodegenerative disorders, and as such will represent a means of exploring interventions for impeding that process.

In summary, amino acids are ascending the staircase towards ever greater significance in their role in initiating neuronal damage to proteins, lipids, mitochondrial cytochromes, and DNA in neurodegenerative disorders. Amino acids also have an essential role as the building blocks of abnormal protein aggregates of neurodegenerative disorders. But, amino acids have clinical value, as in the case of L-DOPA therapy of Parkinson's disease, or in the potential use of antagonists at amino acid (e.g., NMDA) receptors.