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Observations relative to the neurotoxicity and neurotoxic potential of amino acids

Introduction

Amino acids, as essential building blocks of bioactive peptides, polypeptides and proteins, are generally regarded as relatively benign substances. However, experimental findings over the last 25 years have altered this view for selected amino acids which are now recognized as overtly neurotoxic or potentially neurotoxic.

The first amino acid discovered to be a potent neurotoxin was 6-hydroxydopa (6-OHDOPA), a derivative of L-dihydroxyphenylalanine (L-dopa), the substrate for dihydroxyphenethylamine (dopamine, DA) – a neurotransmitter in DA nerves, as well as a substrate for the neurohormones norepinephrine (NE) and epinephrine (Epi). 6-OHDOPA, from the start, was suspect as a neurotoxin because of its chemical similarity to 6-hydroxydopamine (6-OHDA), the potent highly selective toxin for NE and DA neurons. And, as predicted, 6-OHDOPA crossed the blood-brain barrier before being decarboxylated, in part, to 6-OHDA. As such, systemically administered 6-OHDOPA was able to destroy both DA and NE nerves in brain. A description of these neurotoxic properties of 6-OHDOPA is provided in the studies by Kostrzewa and Brus (1998). Neurodegenerative effects of 6-OHDOPA arise from auto-oxidation products, namely semiquinones, quinones and hydroxyindoles. All generate other reactive oxygen species (ROS), such as peroxides, hydroperoxides, superoxides and hydroxyl radicals; as well as reactive nitrogen species (RNS). The ROS and RNS deplete cellular oxygen and inactivate vital cell processes which ultimately deplete cellular energy stores, impair membrane selectivity, inhibit enzyme activities and interfere with protein transcription. Neuronal damage or death is the consequence. Molecular mechanisms by which amino acids like 6-OHDOPA generate ROS and RNS are described in a paper by Metodiewa (1998).

In our environment, particularly in the food chain, 6-OHDOPA is not a species that one is likely to encounter. However, what is described for 6-OHDOPA is not simply an esoteric laboratory finding. The product of tyrosine hydroxylation, L-dopa, is continuously turning over as DA and NE are synthesized in nerves. These reactions inherently generate ROS, and the process is accelerated by Fe^{2+}, which is in DA neurons in the pars compacta of the substantia nigra. It may not be merely coincident that these are neurons that undergo age-related spontaneous degeneration, which is associated with onset and worsening of Parkinsonism. Exogenously administered L-dopa is globally recognized as the most efficacious drug in providing symp-

tomatic relief of Parkinsonian symptoms. L-Dopa therapy, however, may represent a two-edged sword: effectively providing acute relief of symptoms but insidiously accelerating the death of viable DA neurons through generation of ROS at a rate that overwhelms intracellular protective mechanisms. This potential of L-DOPA is described in a paper by VonVoigtlander et al. (1998). Moreover, the clinical relevance of his discussion is more expansive than might have been implied, as we now know that exogenously administered 6-OHDOPA and L-dopa are each beneficially toxic to malignant melanoma cells.

Incidently, 6-OHDOPA and L-dopa are endogenous, not foreign and obscure species. L-Dopa, as mentioned, is a substrate for synthesis of the catecholamines, NE, DA and Epi. 6-OHDOPA was recently discovered to be the active site for amine oxidases in a number of plant and animal species. In fact, in this role 6-OHDOPA exists predominately as a stable quinone.

Cognizant that only a few amino acids are endowed with a high oxidation potential, we immediately can recognize that the aforementioned discussion pertains to a small number of substances. There is, nonetheless, a much larger group of amino acids with potential for producing neurodegeneration. These are the excitotoxins and the class includes glutamate (GLU), aspartate (ASP), kainate, ibotenate, cysteine and many other natural and synthetic analogues. These amino acids appear to produce damage by over-stimulating nerves. We know glutamate to be a flavor-enhancer found in some Chinese and other cuisines. ASP is one of two amino acids that comprises Aspartame. There has been much professional and public debate on the risk posed by these amino acids. Epidemiologic studies have established that two amino acids, β-N-oxalylamino-L-alanine (BOAA) and β-N-methylamino-L-alanine (BMAA), found in chickpeas were the source of slowing progressing neurolathyrism that developed in Pacific islanders that relied on chickpeas as a protein source during World War II. We do not know what other neurotoxic amino acids are in nature.

Neurodegenerative effects of the excitatory amino acids are described in studies by Herrera-Marschitz et al. (1998). These findings establish that ASP, like GLU, is an endogenous neurotransmitter in brain. His talk links the inherent risk of ASP excitation with the discovery that L-dopa or other DA agonists enhance ASP release. Thus, in addition to generating ROS in DA nerves, L-dopa indirectly has an excitatory effect (by virtue of releasing ASP) and has at least a dual risk of accelerating progression of Parkinsonism.

This section is intended to present information on putative risks of several kinds of amino acids and to describe the mechanisms by which these amino acids act. Laboratory studies with these amino acids have provided insight into essential elements of neurophysiology, cellular oxygen metabolism, and calcium metabolism. This knowledge is currently being extrapolated and expanded into the clinical arena, providing a cautionary awareness of potential risks of foods, established medicines, and drugs currently under development.

References

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