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Destruction of catecholamine-containing neurons by 6-hydroxydopa, an endogenous amine oxidase cofactor

R. M. Kostrzewa[1] and **R. Brus**[2]

[1] Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, U.S.A.
[2] Department of Pharmacology, Silesian Academy of Medicine, Zabrze, Poland

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Summary. The amino acid, 6-hydroxydopa (6-OHDOPA), found at the active site of amine oxidases, exists as a keto-enol. Exogenously administered 6-OHDOPA is an excitotoxin like β-N-oxalylamino-L-alanine (BOAA) and β-N-methylamino-L-alanine (BMAA), acting at the non-N-methyl-D-aspartate (non-NMDA) α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor. BMAA and BOAA are causal factors of neurolathyrism in humans. Much exogenously administered 6-OHDOPA is biotransformed by aminoacid decarboxylase (AADC) to the highly potent and catecholamine-(CA) selective neurotoxin, 6-hydroxydopamine (6-OHDA). 6-OHDOPA destroys locus coeruleus noradrenergic perikarya and produces associated denervation of brain by norepinephrine-(NE) containing fibers. Opiopeptides and opioids enhance neurotoxic effects of 6-OHDOPA on noradrenergic nerves, by a naloxone-reversible process. An understanding of mechanisms underlying neurotoxic effects of 6-OHDOPA can be helpful in defining actions of known and newfound amino acids and for investigating their potential neurotoxic properties.

Keywords: 6-Hydroxydopa – 6-Hydroxydopamine – Noradrenergic neurons – Neurotoxicity – Excitatory amino acids

Abbreviations: AADC, aminoacid decarboxylase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; BOAA, β-N-oxalylamino-L-alanine; CA, catecholamine; L-DOPA, L-dihydroxyphenylalanine; DA, dopamine; EAA, excitatory amino acid; 6-OHDOPA, 6-hydroxydopa; 6-OHDA, 6-hydroxydopamine; NE, norepinephrine; BMAA, β-N-methylamino-L-alanine; NMDA, N-methyl-D-aspartate; S.E.M., standard error of the mean

Less than a decade ago, the amino acid 2,4,5-trihydroxyphenylalanine was found to be part of the active site of copper amine oxidase in bovine serum (Janes et al., 1990), existing largely as the ρ-quinone (Pedersen et al., 1992)

(Fig. 1) and present also in amine oxidases of plants, bacteria and yeasts (see Kostrzewa, 1998). This was surprising, in light of the simultaneous discovery that exogenously administered 2,4,5-trihydroxyphenylalanine is an excitatory amino acid (EAA) at the non-N-methyl-D-aspartate (non-NMDA) receptor for α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) (Cha et al., 1991; Olney et al., 1990; Rosenberg et al., 1991); and historically known to be a relatively selective and potent toxin for catecholamine- (CA) containing neurons (Jacobowitz and Kostrzewa, 1971; Sachs and Jonsson, 1972). Older reports refer to 2,4,5-trihydroxyphenylanine as 6-hydroxydopa (6-OHDOPA), while newer reports use the abbreviation topa. In this paper we use 6-OHDOPA, and review its neurotoxic properties, contrast its effects with known overtly toxic or potentially toxic amino acids, and speculate on some potential therapeutic uses for this amino acid.

In the late 1960s the norepinephrine (NE) isomer 6-hydroxydopamine (6-OHDA) was shown to be a potent toxin for CA neurons, with its selectivity being attributable to high affinity for NE and dopamine (DA) transporters, which ultimately promote accumulation of toxic intraneuronal levels of 6-OHDA (Thoenen and Tranzer, 1968). 6-OHDOPA was synthesized specifically because of its accurately predicted ability to cross the blood-brain barrier and be decarboxylated to neurotoxic 6-OHDA and thereby destroy CA neurons in brain (Ong et al., 1969) (Fig. 2).

Evidence of 6-OHDOPA neurotoxicity is evident from (a) reduced CA content, (b) loss of histofluorescent CA nerve terminals, (c) reduced activities of tyrosine hydroxylase and/or dopamine-β-hydroxylase, and (d) reduced numbers of NE or DA transporters in target sites (Jacobowitz and Kostrzewa, 1971; Sachs and Jonsson, 1972). These effects are associated with (e)

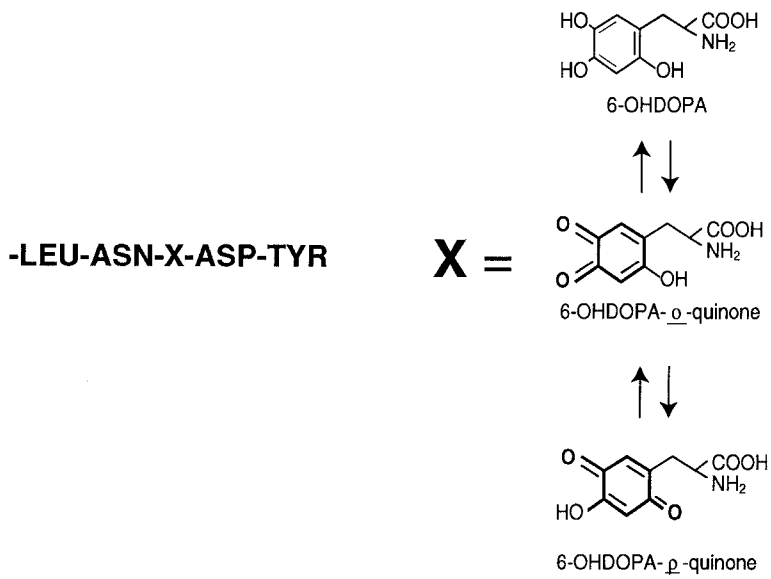

Fig. 1. Active site of bovine serum amine oxidase

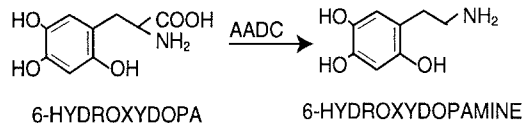

Fig. 2. Chemical structure of the neurotoxin 6-OHDOPA and its biotransformation by aminoacid decarboxylase (AADC) to 6-OHDA

retrograde accumulation of CA in swollen preterminal axons (formaldehyde condensation method), (f) presence of argyrophilic granules with classic silver degeneration staining, and (f) loss of perikarya in CA nuclei (Clark et al., 1978; Kostrzewa and Garey, 1977; Kostrzewa and Harper, 1974). NE neurons were found to be far more sensitive than DA neurons to 6-OHDOPA in both adult and ontogenetically immature animals (Zieher and Jaim-Etcheverry, 1975), and the effect was modulated in a naloxone-reversible process by the opioids morphine, met-enkephalin and leu-enkephalin (Harston et al., 1981).

Many groups have shown that the neurotoxic properties are the consequence primarily of auto-oxidation of 6-OHDOPA or its active metabolite 6-OHDA to semiquinones, quinones, or hydroxyindoles; and consequent generation of peroxide, superoxide, peroxides and other reactive oxidative species (ROS) (see Metodiewa et al., 1989). These ROS (a) lead to formation of tyrosine hydroperoxides and deplete cellular sulfhydryl groups and other active moieties of protein, thereby altering enzyme activities and ionic channel selectivity, while uncoupling oxidative phosphorylation. ROS also (b) produce lipid peroxidation and thereby disrupt membrane semipermeable and (c) alkylate and cross-link DNA (see Pichorner et al., 1995). These multivariate processes lead to cell swelling, reduced cellular stores of energy (ATP), and impaired transcription of proteins. CA neurons are particularly susceptible to injury from ROS.

However, oxidized products of 6-OHDOPA also have affinity for a non-N-methyl-D-aspartate (non-NMDA) receptor (Olney et al., 1990; Rosenberg et al., 1991) that recognizes the ligand α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and the antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (Cha et al., 1991). Excitotoxic effects of 6-OHDOPA-derived ROS primarily affect neurons with AMPA receptors. Thus, 6-OHDOPA is toxic to two classes of neurons, those in which DA or NE are neurotransmitters and those with AMPA receptors.

The ability of 6-OHDOPA to auto-oxidize to a long-lived quinone is a valuable attribute for its role at the active site of amine oxidases in bovine serum (Janes et al., 1990) and in the amine oxidase of bacteria, fungi and plants (see Kostrzewa, 1998). The quinoidal moiety converts an amino group to the aldehyde, en route to a carboxylase end-product.

Nearly 20 years ago Wick et al. (1979) found 6-OHDOPA to be particularly toxic to melanoma cells. More recently, 2,4-dihydroxyphenylalanine (L-DOPA) was shown to target malignant melanoma cells and produce ROS in

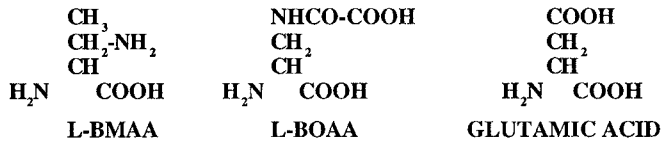

Fig. 3. Other neurotoxic aminoacids: BMAA, BOAA, and glutamic acid

a process mechanistically similar to that of 6-OHDOPA (Morrison et al., 1985). L-DOPA, accordingly, could prove to be a valuable treatment of this deadly cancer.

L-DOPA is the most efficacious of anti-parkinsonian drugs, but its predisposition towards generating ROS in substantia nigra pars compacta DA-containing neurons represents a risk to these cells and potential for L-DOPA accelerating progression of the Parkinsonism. β-N-oxalyl-amino-L-alanine (BOAA) and β-N-methylamino-L-alanine (BMAA), amino acids found in the chickpea, is excitotoxic to neurons with AMPA receptors (Kunig et al., 1994) (Fig. 3) and has been implicated as a causal factor in human neurolathyrism and other neurodegenerative diseases (Meldrum and Garthwaite, 1991; Weiss et al., 1989).

Research findings on 6-OHDOPA and related amino acids demonstrates their potential for producing adverse effects, as well as therapeutic effects in man. It is conceivable that there are other natural amino acids that mimic 6-OHDOPA.

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Authors' address: Dr. R. M. Kostrzewa, Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614-0577, U.S.A.

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