Perinatal Lesioning and Lifelong Effects of the Noradrenergic Neurotoxin 6-Hydroxydopa

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Abstract 6-hydroxydopa (6-OHDOPA) was synthesized with the expectation that it would be able to cross the blood–brain barrier to be enzymatically decarboxylated to 6-hydroxydopamine (6-OHDA), the newly discovered neurotoxin for noradrenergic and dopaminergic neurons. In part, 6-OHDOPA fulfilled these criteria. When administered experimentally to rodents, 6-OHDOPA destroyed peripheral sympathetic noradrenergic nerves and did exert neurotoxicity to noradrenergic nerves in brain—in large part, from its conversion to 6-OHDA. However, the efficacy of 6-OHDOPA was less than that of 6-OHDA; also, 6-OHDOPA was relatively selective for noradrenergic neurons; near-lethal doses of 6-OHDOPA were required to damage dopaminergic nerves; and ultimately, 6-OHDOPA was found to be an agonist at AMPA receptors, thus accounting for more non-specificity. Nevertheless, 6-OHDOPA was found to be a particularly valuable tool in uncovering processes and mechanisms associated with noradrenergic nerve regeneration and sprouting, particularly when administered to perinatal rodents. Also, 6-OHDOPA was a good tool for selective mapping of noradrenergic nerve tracts in brain, since dopaminergic tracts were unaffected and did not interfere with the histofluorescent methodology used for this purpose in the early 1970s. As an experimental research tool, 6-OHDOPA was valuable in a short time-window, but its utility is largely limited because of newer research technologies that provide better means today for nerve tract mapping, and for experimental approaches engaged toward study of processes and mechanisms attending nerve regeneration. AMPA actions of 6-OHDOPA have not been extensively studied, so this avenue may enliven use of 6-OHDOPA in the future.

Keywords 6-hydroxydopa · 6-hydroxydopamine · Nerve regeneration · Nerve sprouting · Noradrenergic nerves · Neuroteratogen · AMPA

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1 Introduction

The norepinephrine (NE) isomer 6-hydroxydopamine (6-OHDA) was initially found to produce long-lasting depletion of norepinephrine in heart (Porter et al. 1963, 1965). Subsequently, 6-OHDA was shown by electron microscopy to overtly destroy noradrenergic nerves (Thoenen and Tranzer 1968a, b) and dopaminergic nerves (Ungerstedt 1968). One limitation of 6-OHDA, however, was its inability to cross the blood–brain barrier (BBB) (Kostrzewa and Jacobowitz 1974).

6-hydroxydopa (6-OHDOPA) was synthesized as an expected pro-toxin and, like levodopa, able to cross the BBB prior to its decarboxylation to 6-OHDA (Ong et al. 1969; Berkowitz et al. 1970; Evans and Cohen 1989, 1993). As expected, 6-OHDOPA produced norepinephrine (NE) depletion in brain and peripheral tissues (Jonsson and Sachs 1973; Kostrzewa and Jacobowitz 1972, 1973; Richardson and Jacobowitz 1973) and subsequently was shown by loss of tyrosine hydroxylase activity and by histochemical, electronmicroscopic, and silver degeneration staining to overtly destroy noradrenergic nerves (Jacobowitz and Kostrzewa 1971; Kostrzewa and Harper 1974, 1975; Sachs et al. 1973; Kostrzewa et al. 1978; Tohyama et al. 1974; Toyama et al. 1974), with preference for noradrenergic perikarya in caudal locus coeruleus (LC) (Clark et al. 1979). Peripheral noradrenergic (i.e., sympathetic) nerves, in contrast to central noradrenergic nerves, appear to fully recover from 6-OHDOPA damage (Kostrzewa and Jacobowitz 1972; Sachs and Jonsson 1972a, b) and can be protected from damage by administering a peripherally acting dopa decarboxylase inhibitor, namely carbidopa (Kostrzewa et al. 2000).

2 Mechanism of Action of 6-OHDOPA

The destructive effects of 6-OHDOPA on noradrenergic and dopaminergic neurons are attributable to its conversion to 6-OHDA, which is known to auto-oxidize to ortho- and para-quinones, aminochromes, and hydroxyindoles (Adams et al. 1972;

Blank et al. 1972; Saner and Thoenen 1971; Senoh and Witkop 1959; Wehrli et al. 1972)—reactive species leading to formation of intraneuronal peroxide (Heikkila and Cohen 1971, 1972a, b), superoxide, and hydroxyl radical (Cohen and Heikkila 1974; Heikkila and Cohen 1973).

3 6-OHDOPA as a Neuroteratogen

When administered to perinatal rats, 6-OHDOPA (60 μg/g at P0 + P2 + P4) produced lifelong alterations in noradrenergic innervation of brain (Kostrzewa 1975; Kostrzewa and Garey 1976). The nucleus LC providing the major portion of noradrenergic innervation of dorsal brain was directly damaged, with there being loss of one-third of the approximately 1500 perikarya, and with half the numbers of cells in the caudal portion of the LC undergoing degeneration (Clark et al. 1979). Hippocampal noradrenergic innervation was reduced by >95 %, and neocortex, by ~70 % (Kostrzewa and Harper 1974, 1975; Kostrzewa 1975; Kostrzewa and Garey 1976, 1977). As a consequence of damage to the dorsal bundle, the major ascending noradrenergic tract to forebrain, noradrenergic fibers projecting to regions near the LC per se sprouted and hyperinnervated midbrain, pons, medulla, and cerebellum (Jaim-Etcheverry and Zieher 1977; Jaim-Etcheverry et al. 1975; Kostrzewa and Harper 1974, 1975; Kostrzewa 1975; Kostrzewa and Garey 1976, 1977; Kostrzewa et al. 1978; 1982; Zieher and Jaim-Etcheverry 1979). This reactive sprouting resulted in as much as a twofold increase in numbers of fibers' innervation of caudal brain regions. In contrast, innervation to hypothalamus was slightly altered. The pairing of noradrenergic hypoinnervation of forebrain with noradrenergic hyperinnervation of hindbrain is replicated by knife cuts of the dorsal bundle shortly after birth, suggesting that hindbrain hyperinnervation is an outcome of forebrain noradrenergic hypoinnervation (Klisans-Fuenmayor et al. 1986; Kostrzewa et al. 1988).

This spectrum of effects is replicated (1) by single 6-OHDOPA treatment of rats at birth, also (2) by prenatal 6-OHDOPA, administered to pregnant rats at G14 or later, and (3) by prenatal 6-OHDOPA to pregnant mice at G13 or later (Jaim-Etcheverry et al. 1975; Kostrzewa 2007; Kostrzewa et al. 1978; Zieher and Jaim-Etcheverry 1973, 1975a, b). When 6-OHDOPA is administered solely at P3, there is an absence of noradrenergic sprouting to cerebellum. Described perinatal 6-OHDOPA effects on noradrenergic neurons persist throughout life (Jaim-Etcheverry et al. 1975; McLean et al. 1976, 1980; Zieher and Jaim-Etcheverry 1973, 1975a, b). A single 6-OHDOPA treatment at P5 fails to produce noradrenergic hyperinnervation of midbrain, while single 6-OHDOPA treatment as late as P14 still produces hyperinnervation of pons–medulla (Kostrzewa and Garey 1977).

Agonists at μ-opioid receptors (i.e., morphine, met-/leu-enkephalin, beta-endorphin, and d-ala-enkephalinamide) appeared to enhance perinatal 6-OHDOPA neurotoxicity and thereby enhance noradrenergic hyperinnervation of hindbrain and cerebellum—the effect being attenuated by the opioid receptor

antagonist naloxone (Harston et al. 1980, 1981; Kostrzewa and Klisans-Fuenmayor 1984).

Despite the consequences of 6-OHDOPA on noradrenergic innervation, dopaminergic innervation to neostriatum is unaltered through the duration of postnatal ontogeny and for the life span by perinatal low-dose 6-OHDOPA (Kostrzewa and Garey 1976); at high-dose perinatal 6-OHDOPA, the tuberoinfundibular dopaminergic tract (Lin et al. 1993) is more susceptible to damage than the nigrostriatal dopaminergic tract (Nomura and Segawa 1979). Also, serotoninergic nerves are resistant to 6-OHDOPA neurotoxicity (Richardson et al. 1974).

Perinatal 6-OHDOPA treatment initially damaged sympathetic noradrenergic nerves innervating peripheral organs (i.e., heart, salivary glands), but by maturity all organs were fully innervated.

6-OHDOPA actions on noradrenergic neurons have been reviewed elsewhere (Kostrzewa 1988, 1988, 2014).

4 6-OHDOPA Agonist Action at AMPA Receptors

Although 6-OHDOPA was shown, in 1976, to produce more of an excitatory action than glutamate on frog spinal neurons (Biscoe et al. 1976), not until 1990 was it discovered that 6-OHDOPA exerts agonist action at alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA-R) (Cha et al. 1991; Kunig et al. 1994a, b; Olney et al. 1990). Actually, 6-OHDOPA-quinone is the suspected agonist (Aizenman et al. 1990, 1992; Rosenberg et al. 1991). AMPA-R activity would represent a confound to the actions of 6-OHDOPA per se on noradrenergic neurons.

5 Non-specific Effects of Perinatal 6-OHDOPA

In rats treated with perinatal 6-OHDOPA, cholineacetyltransferase activity is reduced in brainstem (Jaim-Etcheverry et al. 1975), and atropine-induced locomotor activity at P20 and P50 is enhanced, while pilocarpine catalepsy is abated (Nomura and Segawa 1979; Nomura et al. 1979). This cholinergic subsensitivity is reflected in the B_{max} for [^{3}H]QNB (quinuclidinyl benzilate) binding at muscarinic receptor sites in mesolimbic and striatal brain regions and also in heart (Nomura et al. 1979).

High-dose 6-OHDOPA treatment is associated with the production of methemoglobinemia (Corrodi et al. 1971), which of itself promotes in vivo formation of 6-OHDOPA from tyrosine, a process enhanced by hydrogen peroxide formation (Agrup et al. 1983) and known to increase after 6-OHDOPA treatment.

6 Summary

6-OHDOPA was envisioned as an experimental tool, able to cross the BBB to be decarboxylated to 6-OHDA, and thus exert effects on noradrenergic and/or dopaminergic nerves in brain. By this means, 6-OHDA effects on brain could be realized without the necessity to otherwise inject 6-OHDA directly into brain—since 6-OHDA does not cross the BBB. However, the neurotoxicity action (i.e., efficacy) of 6-OHDOPA is far less than that of 6-OHDA. Moreover, as a means of minimizing global effects, experimental 6-OHDA is generally applied to specific brain nuclei or specified tracts, not intraventricularly or intracisternally. Consequently, the overall utility of 6-OHDOPA is greatly restricted in biomedical research.

The non-specific effects of 6-OHDOPA, namely AMPA-R agonist activity by non-enzymatically formed 6-OHDOPA-quinone, and the methemoglobinemia arising from 6-OHDOPA and its quinone, further restrict the usefulness of 6-OHDOPA as an experimental tool.

Nevertheless, the early work with 6-OHDOPA did validate its role as a relatively selective noradrenergic neurotoxin, and the actions of 6-OHDOPA in perinates led to discovery of processes and mechanisms associated with nerve sprouting and nerve regeneration. Conceivably, action at the AMPA-R could still be advantageous in 6-OHDOPA use as a research tool.

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