Perinatal 6-Hydroxydopamine to Produce a Lifelong Model of Severe Parkinson's Disease

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Abstract The classic rodent model of Parkinson's disease (PD) is produced by unilateral lesioning of pars compacta substantia nigra (SNpc) in adult rats, producing unilateral motor deficits which can be assessed by dopamine (DA) D_2 receptor (D_2-R) agonist induction of measurable unilateral rotations. Bilateral SNpc lesions in adult rats produce life-threatening aphagia, adipsia, and severe motor disability resembling paralysis—a PD model that is so compromised that it is seldom used. Described in this paper is a PD rodent model in which there is bilateral 99 % loss of striatal dopaminergic innervation, produced by bilateral intracerebroventricular or intracisternal 6-hydroxydopamine (6-OHDA) administration to perinatal rats. This procedure produces no lethality and does not shorten the life span, while rat pups continue to suckle through the pre-weaning period; and eat without impairment post-weaning. There is no obvious motor deficit during or after weaning, except with special testing, so that parkinsonian rats are indistinguishable from control and thus allow for behavioral assessments to be conducted in a blinded manner. L-DOPA (L-3,4-dihydroxyphenylalanine) treatment increases DA content in striatal tissue, also evokes a rise in extraneuronal (i.e., in vivo microdialysate) DA, and is able to evoke dyskinesias. D_2-R agonists produce effects similar to those of L-DOPA. In addition, effects of both D_1- and D_2-R agonist effects

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on overt or latent receptor supersensitization are amenable to study. Elevated basal levels of reactive oxygen species (ROS), namely hydroxyl radical, occurring in dopaminergic denervated striatum are suppressed by L-DOPA treatment. Striatal serotoninergic hyperinnervation ensuing after perinatal dopaminergic denervation does not appear to interfere with assessments of the dopaminergic system by L-DOPA or D_1- or D_2-R agonist challenge. Partial lesioning of serotonin fibers with a selective neurotoxin either at birth or in adulthood is able to eliminate serotoninergic hyperinnervation and restore the normal level of serotoninergic innervation. Of all the animal models of PD, that produced by perinatal 6-OHDA lesioning provides the most pronounced destruction of nigrostriatal neurons, thus representing a model of severe PD, as the neurochemical outcome resembles the status of severe PD in humans but without obvious motor deficits.

Keywords Parkinson's disease · 6-hydroxydopamine · 6-OHDA · Animal model · Nigrostriatal tract · Dopamine · Serotonin · Receptor supersensitivity

Contents

1 Introduction

Parkinson's disease (PD), a neurodegenerative disorder characterized by age-related spontaneous degeneration of pars compacta substantia nigra (SNpc) dopaminergic neurons, has become readily amenable to animal modeling because of the discovery of relatively selective neurotoxins for dopaminergic neurons. The most commonly used of such neurotoxins are (1) the mitochondrial complex I inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium ion (MPP^+) (Langston et al. 1984b), also (2) its metabolic precursor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston and Ballard 1984; Langston et al. 1984a; Manning-Bog and Langston 2007; Pasquali et al. 2014), (3) daily administration of rotenone, another complex I inhibitor (Ernster et al. 1963; Gutman et al. 1970) which destroys nigrostriatal neurons (Betarbet et al. 2000; Sherer et al. 2002, 2003), and (4) 6-hydroxydopamine (6-OHDA) which can be rendered dopaminergic selective when co-administered with desipramine, a ligand inhibitor of the norepinephrine transporter (Smith et al. 1973). Unilateral 6-OHDA lesioning of rodent SNpc is commonly used to model PD (Ungerstedt 1968), since motor behavior is maintained and vital behaviors persist after lesioning (e.g., eating, drinking, and grooming) (Ungerstedt 1971a). Putative anti-parkinsonian agents, typically dopamine (DA) D_2 receptor (D_2-R) agonists tested in this model, evoke unilateral rotational activity contralateral to the lesioned side (Ungerstedt 1971c)—an event related to the development of D_2-R supersensitivity (D_2-RSS) on the lesioned side (Ungerstedt 1971b, c). In black mice, MPTP, administered systemically, crosses the blood–brain barrier and is metabolized to MPP^+ which selectively destroys SNpc dopaminergic neurons bilaterally. Nevertheless, a reasonable number of SNpc neurons survive MPTP treatment, as well as dopaminergic innervation of striatum. White rats are virtually unaffected by MPTP and MPP^+, largely limiting these neurotoxins to black mice or primate modeling of PD.

Severe SNpc bilateral lesioning would represent an ideal rodent model for many experimental studies (Zigmond and Stricker 1984). Unfortunately such a lesion produced by intra-nigral 6-OHDA treatment of adult rodents produces aphagia, adipsia, cessation of grooming, and virtual motor paralysis (Ungerstedt 1971a; Zigmond and Stricker 1972). Rodents die within a few days except with extraordinary measures to maintain hydration, body heat, and cleanliness. In time, behavioral recovery from partial nigral lesions can occur (Neve et al. 1982; Dravid et al. 1984; Altar et al. 1987). These liabilities of bilateral 6-OHDA lesioning of rodents are overcome by administering 6-OHDA intracerebroventricularly or intracisternally to rodents—rats in particular—within a few days of birth. This treatment is non-lethal, virtually all rats survive and continue to eat, drink, and ambulate. In adulthood, except for a slight diminishment in body mass, 6-OHDA-lesioned rats are indistinguishable from control non-lesioned rats except by special testing (Breese et al. 1984a, b; Hamdi and Kostrzewa 1991).

The neontally 6-OHDA (n6-OHDA)-lesioned rat is described in detail in this paper as a valuable model of severe PD, characterized by ~99 % loss of SNpc and associated striatal dopaminergic denervation but with good motor activity (Kostrzewa et al. 1998). The elements of DA D_1-R sensitization are considered, as well as the slight influence on D_2-R sensitization and the involvement of serotonin (5-HT) receptor sensitization, namely 5-HT_{2C}-R, on dopaminergic systems. Effects of L-DOPA (L-3,4-dihydroxyphenylalanine) are described in terms of partial restoration of striatal tissue content of DA and influence on extraneuronal (i.e., in vivo microdialysate) levels of DA and L-3,4-dihydroxyphenylacetic acid (DOPAC) levels. The influence of DA-lesioning and L-DOPA treatment on intraneuronal and extraneuronal ROS, namely hydroxyl radical (HO·), is likewise described. The overall composite of neurochemical and behavioral effects of 6-OHDA, and its partial negation by L-DOPA, provide convincing evidence for the use of n6-OHDA rats as a near-ideal model of severe PD.

2 Nigrostriatal Dopaminergic Nerve Damage by Neonatal 6-OHDA

Neonatal 6-OHDA (n6-OHDA), either by a non-central route (sc, ip) (Jonsson and Sachs 1976; Jonsson et al. 1974; Sachs and Jonsson 1972, 1975) or central route (intracisternal) (Breese and Traylor 1972), produces marked destruction of both noradrenergic and dopaminergic nerves in brain. By pretreating with desipramine, protection is conferred on noradrenergic nerves and thereby 6-OHDA becomes relatively selective, producing predominately dopaminergic nerve destruction (Smith et al. 1973). While there is partial preservation of dopaminergic perikarya in the ventral tegmental nucleus (VTA) after 6-OHDA (Snyder et al. 1986; Fernandes Xavier et al. 1994), destruction of dopaminergic perikarya in substantia nigra (SN) is near total (Berger et al. 1985; Fernandes Xavier et al. 1994). As a consequence, dopaminergic innervation of VTA targets—namely septum, nucleus accumbens, and frontal cortex—is reduced (Luthman et al. 1990a), while dopaminergic innervation of the SN target, namely striatum, is near total (Snyder et al. 1986; Descarries et al. 1992). The extent of dopamine (DA) depletion in the respective brain regions is reflective of the degree of dopaminergic denervation, and the described effects of n6-OHDA are lifelong (Breese and Traylor 1972; Breese et al. 1984a, 1994; Breese and Breese 1998; Stachowiak et al. 1984).

Despite the drastic loss of dopaminergic innervation of brain by n6-OHDA treatment, survival is not altered. Also, overt behavioral effects are not obvious, although 6-OHDA-lesioned rats have slightly reduced body weight (Bruno et al. 1984). However, the aphasia and adipsia observed in rats lesioned as adults with 6-OHDA do not occur in rats lesioned neonatally with 6-OHDA (Breese and Traylor 1972; Smith et al. 1973). Sensorimotor function is maintained (Weihmuller and Bruno 1989a, b; Potter and Bruno 1989).

Nevertheless, with special testing there are "behavioral" deficits that can be revealed in adulthood in n6-OHDA-lesioned rats, analogous to deficits observed in adulthood 6-OHDA-lesioned rats (Papadeas and Breese 2014). n6-OHDA-lesioned rats, in adulthood, do not drink a sucrose solution (Smith et al. 1973); are unable to acquire an avoidance response during aversive learning (Smith et al. 1973; Shaywitz et al. 1976b; Pappas et al. 1980; Raskin et al. 1983; Whishaw et al. 1987); display skilled motor deficits (Whishaw et al. 1987); lack the ability for high-rate operant responding (Takeichi et al. 1986; Stellar et al. 1988); and have acquisition deficits in operant responding (Heffner and Seiden 1983).

The overall preservation of function in n6-OHDA-lesioned rats is considered to be related to increased DA synthesis by surviving dopaminergic nerves (Molina-Holgado et al. 1994), also increased storage of DA (Reader and Dewar 1999), and release of greater amounts of DA (Castañeda et al. 1990a, b). Notably, further adulthood reduction of DA in the n6-OHDA-lesioned rats, either by impairing tyrosine hydroxylase (TOH) activity or by adulthood 6-OHDA treatment, produces deficits resembling that observed by single adulthood 6-OHDA treatment (Rogers and Dunnett 1989b).

The most obvious change from controls is the absence of catalepsy following adulthood treatment with DA receptor (DA-R) antagonists (Bruno et al. 1984; Duncan et al. 1987). Also, n6-OHDA-lesioned rats are hyperactive in adulthood and have been used as an animal model of attention-deficit hyperactivity disorder (ADHD), since amphetamine or methylphenidate suppresses hyperactivity in these rats versus their promotion of hyperactivity in intact control rats (Shaywitz et al. 1976a, b; see Kostrzewa et al. 2008; Kostrzewa et al. 2016).

One negative aspect of n6-OHDA-lesioned rats is the potential for L-DOPA induction of self-injurious behavior (SIB). Haloperidol partially attenuates L-DOPA-induced SIB (Breese et al. 1984a, b, 1985b), while D_1-R antagonists fully block the effect (Breese et al. 1985a, 1989, 1990a, b; Criswell et al. 1992). Notably, a D_1-R agonist, alone, does not evoke SIB, nor does a D_2-R agonist, alone, but the combination of a D_1-R agonist with a D_2-R agonist can evoke SIB (Breese et al. 1985a).

It is noteworthy that in rats treated with haloperidol in drinking water for 11 months, to model tardive dyskinesia (Huang et al. 1997), there is a much higher level of haloperidol-evoked VCMs in n6-OHDA-lesioned rats versus intact control rats. Also, when haloperidol treatment is terminated for 9 months, 5-HT_2-R antagonists abate the high level of VCMs in n6-OHDA-lesioned rats, while D_1-R antagonists do not do so (Huang et al. 1997; see Kostrzewa and Brus 2016).

3 Striatal DA-R After n6-OHDA

3.1 DA D_1-R Number

The relative number of striatal DA D_1 receptors (D_1-R) following n6-OHDA treatment is reported to be slightly increased (Broaddus and Bennett 1990),

unchanged (Breese et al. 1987; Luthman et al. 1990b; Duncan et al. 1993; Gong et al. 1994), or slightly decreased (Dewar et al. 1990, 1997; Molina-Holgado et al. 1995). Regardless, there is no change in the relative number of both high-affinity D_1-R and low-affinity D_1-R (Gong et al. 1994).

3.2 DA D_2-R Number

When striatal D_2-R number was assessed by [^{3}H]spiperone binding, there was no change from control in the n6-OHDA-lesioned rats (Breese et al. 1987; Duncan et al. 1987; Kostrzewa and Hamdi 1991). However, with [^{3}H]raclopride binding striatal, D_2-R was found to be increased at 1–3 months in rostral striatum of n6-OHDA-lesioned rats (Dewar et al. 1990); and increased at a later time, throughout the striatum (Radja et al. 1993b).

Because the D_1-R class includes both D_1-R and D_5-R subclasses, and because the D_2-R class includes D_2-R, D_3-R and D_4-R subclasses (see Strange 1993), it is possible that different subclasses of these receptors are altered, in different ways in each subregion of brain, and according to 6-OHDA dosage. Accordingly, it is difficult to ascribe a particular behavior alteration with a specific receptor subclass in any defined brain region. With this caveat, it appears that alterations in the D_4-R subclass in striatum and nucleus accumbens are more closely associated with the hyperactivity of n6-OHDA-lesioned rats; and D_4-R antagonists attenuate the hyperactivity (Zhang et al. 2002a, b).

4 DA-R Sensitization Status After n6-OHDA

4.1 Latent DA D_1-R Sensitization

Regardless of whether DA D_1-R number is altered in n6-OHDA-lesioned rats, there is no obvious increase in stereotypic and locomotor effects of an initial D_1-R agonist treatment. However, with repeated D_1-R agonist treatments, there is ultimate development of D_1-RSS (Breese et al. 1985a, b), as evidenced by the fact that repeated D_1-R agonist treatments either during postnatal ontogeny (Hamdi and Kostrzewa 1991; Gong et al. 1993a) or in adulthood (Breese et al. 1987) produce an abnormal increase in the stereotypic (nucleus accumbens/striatum sites) and locomotor (nucleus accumbens site) response. The D_1-RSS produced by ontogenetic D_1-R agonist treatments is incomplete, as additional D_1-R agonist treatments produce further D_1-R agonist supersensitization (Gong et al. 1993a). The development of RSS is designated as a “priming” phenomenon (Breese et al. 1987). D_1-RSS is not accompanied by an increase in the D_1-R number (i.e., B_{max}) or affinity (K_d) (Hamdi and Kostrzewa 1991); nor in the percentage of high-affinity or low-affinity

receptors, nor by a change in DA-stimulated adenylate cyclase activity (Gong et al. 1994). However, D_1-RSS is permanent (Criswell et al. 1989; Kostrzewa and Gong 1991).

Repeated pre-weanling D_2-R agonist treatments also prime (i.e., supersensitize) D_1-R in adulthood for locomotor and stereotyped effects (Criswell et al. 1989).

4.2 Overt DA D_1-R Sensitization

In n6-OHDA-lesioned rats, the first D_1-R agonist dose produces a marked increase in the numbers of vacuous chewing movements (VCMs) (i.e., oral activity = oral dyskinesia) versus the D_1-R agonist response in non-lesioned control rats (Kostrzewa and Gong 1991). Pre-weaning D_1-R agonist treatments, moreover, promotes an even further increase in the adulthood D_1-R induction of VCMs, indicating further sensitization, priming, of D_1-R associated with VCMs (Gong et al. 1993a).

4.3 Reliance of D_1-RSS on the Serotoninergic System

This overt D_1-RSS is accompanied by simultaneous serotonin (5-HT) receptor supersensitization (RSS) (Gong and Kostrzewa 1992; el Mansari et al. 1994), which appears to reside primarily with the 5-HT_{2C}-R subtype (Gong et al. 1992). This 5-HT_{2C}-RSS and its inductive effect on VCMs are not abated by D_1-R antagonists. In contrast, D_1-R induction of VCMs is abated by 5-HT_2-R antagonists, indicating that D_1-R-mediated effects are reliant of 5-HT_2 receptor effects (Gong and Kostrzewa 1992; Gong et al. 1992, 1993b), residing at least in part in ventral striatum (Plech et al. 1995). In fact, the development of overt D_1-RSS after n6-OHDA is suppressed if 5-HT innervation is largely destroyed by the serotoninergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), administered simultaneously with n6-OHDA administration (Brus et al. 1994), or when the serotoninergic hyperinnervation is eliminated in adulthood by 5,7-DHT treatment (unpublished).

Development of 5-HT_2-RSS occurs when n6-OHDA treatment produces a loss of striatal DA ≥ 97 %, but not when the loss of striatal DA is ≤88 % (Gong et al. 1993b) or when n6-OHDA treatment is later than three days of post-birth (Kostrzewa et al. 1993a). In fact, 5-HT_2-RSS can persist when D_1-RSS does not exist in n6-OHDA-lesioned rats (Gong et al. 1993b; Kostrzewa et al. 1993a). Therefore, serotoninergic adaptations to n6-OHDA treatment may account for multiple behavioral interactions, as well as responsiveness to DA-R and 5-HT-R agonists (Luthman et al. 1991; Kostrzewa et al. 1993b).

4.4 DA D_2-R Sensitization

In contrast to the noted priming of D_1-R in rats lesioned neonatally with 6-OHDA, there is no obvious sensitization, overt or latent, of D_2-R (Criswell et al. 1989). However, when the D_2-R antagonist spiperone is administered in adult n6-OHDA-lesioned rats, there is enhanced oral activity (VCMs) compared to unlesioned controls (Hamdi and Kostrzewa 1991). Repeated pre-weanling D_2-R agonist treatments in n6-OHDA-lesioned rats sensitize for D_2-R agonist-induced vertical jumping at 3 weeks of age or later (Kostrzewa and Kostrzewa 2012). However, ontogenetic quinpirole treatments fail to prime for D_2 agonist-enhancement of locomotor activity in adult n6-OHDA-lesioned rats (Brus et al. 2003). Descriptions of DA D_1-R and D_2-R sensitization in n6-OHDA-lesioned rats are discussed in detail in an earlier report (Kostrzewa 1995).

5 Serotonin Neural Adaptations to n6-OHDA Lesioning of Nigrostriatal Neurons

The relative dopaminergic denervation of striatum attending n6-OHDA treatment is accompanied by an elevation of striatal serotonin (5-hydroxytryptamine, 5-HT) levels in adulthood (Breese et al. 1984a; Stachowiak et al. 1984)—an outcome occurring only if striatal DA is depleted by >80 % (Towle et al. 1989; Gong et al. 1993b) and when 6-OHDA is administered within the first ten days of post-birth (Kostrzewa et al. 1993a). The increase in striatal 5-HT is associated with increased striatal synaptosomal uptake of [^{3}H]5-HT (Stachowiak et al. 1984) or other ligands of the 5-HT transporter (Molina-Holgado et al. 1994; Soucy et al. 1994; Descarries et al. 1995).

Elevated striatal 5-HT content is attributable to serotoninergic terminal hyperinnervation of striatum (Snyder et al. 1986; Luthman et al. 1987; Towle et al. 1989)—mainly in rostral striatum (Stachowiak et al. 1984; Snyder et al. 1986; Luthman et al. 1987; Descarries et al. 1992), a near doubling of serotoninergic fiber number in this region in n6-OHDA-lesioned rats (Mrini et al. 1995). In caudal striatum, serotoninergic innervation is increased only by ~20 % (Mrini et al. 1995), thereby inverting the normal gradient of increasing striatal rostro-caudal innervation (Ternaux et al. 1977; Soghomonian et al. 1989). Serotoninergic hyperinnervation develops fully by 2–3 months of post-birth (Dewar et al. 1990).

By retrograde tracing of horseradish peroxidase, it appears that medial and dorsal raphe perikarya, which normally provide serotoninergic innervation to caudal striatum, largely account for serotoninergic hyperinnervation of rostral striatum (Snyder et al. 1986), and still retaining the typical 10 % ratio of synaptic to non-synaptic striatal serotoninergic terminations (Descarries et al. 1992).

While serotoninergic hyperinnervation does not produce an elevation in extraneuronal 5-HT levels (Jackson and Abercrombie 1992), serotoninergic

hyperinnervation is associated with reduced acetylcholine release (Jackson et al. 1988). Serotoninergic hyperinnervation does not preserve functions that are impaired by dopaminergic denervation, since perinatal treatment with the serotoninergic neurotoxin 5,7-DHT does not produce greater functional impairment (Breese et al. 1978; Bruno et al. 1987).

As determined by quantitative ligand-binding autoradiography of serotoninergic hyperinnervated striatum, there is an approximate increase in numbers of 5-HT_{1B} (+30 %), 5-HT_{1nonAB} (i.e., 5-HT_{2C}, 5-HT_{1D}, 5-HT_{1E}) (+40 %), and 5-HT_{2A} receptor number, but no change in 5-HT_{1A}-R number (Radja et al. 1993a). Moreover, elevations in 5-HT_{1B}-R occurred also in globus pallidum and substantia nigra (i.e., striatopallidal and striatonigral pathways); elevations in 5-HT_{1nonAB}-R were observed in substantia nigra (i.e., striatonigral pathway) (Radja et al. 1993a). GABA (gamma-aminobutyric acid), cholinergic (Jackson et al. 1993; Kostrzewa and Neely 1993), and other systems are altered in adulthood in n6-OHDA-lesioned rats (see Papadeas and Breese 2014).

6 L-DOPA Effects on DA Neurochemistry and Reactive Oxygen Species in n6-OHDA-Lesioned Rats

In vitro DA in high concentration is overtly toxic to cells in culture, possibly by virtue of its auto-oxidation to DA-hydroquinone, DA-o-quinone, DA-p-quinone, adrenochrome, and other analogs including DA-semiquinone which recycles in a schema to generate additional ROS including hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{-\cdot}$), and hydroxyl radical (HO·) (Senoh and Witkop 1959a, b; Senoh et al. 1959; Graham et al. 1978; Kaur and Halliwell 1996; Bindoli et al. 1999; Segura-Aguilar 2001; Segura-Aguilar and Paris 2014).

There is thus the quandary as to whether L-DOPA, the most efficacious drug for treatment of PD, might pose the risk of promoting dopaminergic cell death by virtue of greater intraneuronal formation of neurotoxic ROS, while acutely and simultaneously alleviating neuromuscular symptoms. Accordingly, a series of studies was conducted in the n6-OHDA-lesioned rats to explore this possible outcome.

6.1 L-DOPA Effects in Striatal Tissue of n6-OHDA-Lesioned Rats

Intact and n6-OHDA-lesioned rats at ten weeks of post-birth were acutely treated with L-DOPA (60 mg/kg i.p.) subsequent to carbidopa (12.5 mg/kg i.p., 30 min) pretreatment. Following ketamine–xylazine anesthetization and surgical implantation of a cannula guide, salicylic acid (8 micromoles) was injected intracerebroventricularly so that HO· could be detected in striatal tissue as the salicylate spin

trap products, 2,3- and 2,5-dihydroxybenzoic acid (2,3-DHBA; 2,5-DHBA), 45 min after the prior L-DOPA treatment (Kostrzewa et al. 2000). 2,5-DHBA is reflective of cytochrome P450 metabolism (Giovanni et al. 1995; Dajas-Bailador et al. 1998).

The following was determined.

6.2 Striatal DA and DOPAC

Endogenous DA and DOPAC in striatal tissue of n6-OHDA-lesioned rats at 10 weeks of post-birth were reduced by ~99 % (Kostrzewa et al. 2000), which was shown in related studies to represent an equivalent reduction in TOH immunoreactive fibers and DA transporters (DATs) in striatum, along with a similar loss of SNpc perikarya (Berger et al. 1985; Snyder et al. 1986; Descarries et al. 1992; Fernandez Xavier et al. 1994).

6.3 Striatal 5-HT and 5-HIAA

Endogenous 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in neostriatal tissue of n6-OHDA-lesioned at 10 weeks of post-birth were elevated by ~75 and ~50 %, respectively (Kostrzewa et al. 2000)—shown in related studies to represent serotoninergic hyperinnervation of striatum (Stachowiak et al. 1984; Berger et al. 1985; Snyder et al. 1986; Descarries et al. 1992).

6.4 L-DOPA Effects on Striatal DA and DOPAC

In intact control rats, L-DOPA treatment elevated striatal DOPAC content by 100 % but had no effect on striatal DA content—indicating rapid metabolism of newly formed DA to DOPAC. In n6-OHDA-lesioned rats, L-DOPA produced (1) ~30-fold elevation in striatal DA, to a level equivalent to ~25 % of that of untreated intact striatum, and (2) ~30-fold elevation in striatal DOPAC, to a level equivalent to ~100 % of that of untreated intact striatum (Kostrzewa et al. 2000).

6.5 L-DOPA Effects on Striatal 5-HT and 5-HIAA

In intact control rats, L-DOPA treatment reduced endogenous striatal 5-HT content by ~30 %, while elevating 5-HIAA by ~25 %. This is likely reflective of L-DOPA uptake by serotoninergic fibers followed by DA formation and consequent displacement of 5-HT by newly formed DA, which would be a false-transmitter in

serotoninergic nerve terminals (Kannari et al. 2000). 5-HIAA elevation would reflect rapid metabolism of displaced 5-HT (Kostrzewa et al. 2000).

6.6 Striatal HO·

Tissue content of HO·, as indicated by 2,3-DHBA and 2,5-DHBA contents, was elevated more than 3-fold in the striatum of n6-OHDA-lesioned rats at ten weeks of post-birth, versus intact control striatum (Kostrzewa et al. 2000). This finding implies that DA would normally maintain low tissue levels of HO·; dopaminergic denervation is accompanied by greater HO· formation/retention.

6.7 L-DOPA Effects on Striatal Tissue of n6-OHDA-Lesioned Rats

L-DOPA treatment reduced HO· content in intact control striatum, as indicated by ~60 % reduction in 2,3-DHBA and ~95 % reduction in 2,5-DHBA levels. In n6-OHDA-lesioned rats, L-DOPA similarly reduced 2,5-DHBA by ~50 % but failed to alter 2,3-DHBA content. These findings similarly indicate that L-DOPA-derived DA was slightly neuroprotective (Kostrzewa et al. 2000, 2002).

6.8 Summary on Striatal Tissue

In the n6-OHDA-lesioned rat model of PD, dopaminergic denervation of striatum is associated with a marked elevation of tissue HO·, while L-DOPA treatment is acutely associated with a slight decrease in enzymatically formed HO· (i.e., 2,5-DHBA). This implies that DA is reflective of a neuroprotective species, while its relative absence leads to greater ROS formation.

7 Striatal Microdialysates of n6-OHDA-Lesioned Rats

L-DOPA effects were also assessed by in vivo microdialysis in the striatum of awake and freely moving intact and n6-OHDA-lesioned rats. In these rats in adulthood, basal levels of striatal extraneuronal levels of DA and DOPAC were much lower, as expected since there was far less striatal dopaminergic innervation in the lesioned rats (Kostrzewa et al. 2005; Nowak et al. 2010). However, basal extraneuronal levels of 2,3- and 2,5-DHBA in the striatum of n6-OHDA-lesioned

rats were elevated from that of intact control rats by 2-fold and 3-fold, respectively (Nowak et al. 2010). This change is comparable to that observed for striatal tissue levels of 2,3- and 2,5-DHBA in n6-OHDA-lesioned rats.

L-DOPA administration (100 mg/kg i.p.; carbidopa, 12.5 mg/kg i.p., 30 min pretreatment) increased the striatal microdialysate level of DA in intact control rats by ~5-fold and in n6-OHDA-lesioned rats by ~25-fold. Consequently, the attained extraneuronal level of DA following L-DOPA was actually ~3 times higher in lesioned versus intact controls (Abercrombie et al. 1990; Kostrzewa et al. 2005). In the striatum of n6-OHDA-lesioned rats, there is a relative dopaminergic denervation and near-total absence of DATs. Also in striatum, DA exocytosis is predominately volume transmission versus synaptic transmission. Therefore, once DA is released from the few remaining dopaminergic terminals in n6-OHDA-lesioned rats, there is virtually no recapture of release DA—accounting for the high extraneuronal levels after L-DOPA (Fuxe et al. 1988). In contrast, because the total amount of DOPAC formed from DA in the striatum of intact rats is so much greater than that for n6-OHDA-lesioned rats, L-DOPA-induced extraneuronal levels of DOPAC are much higher in intact control than in n6-OHDA-lesioned rats (Nowak et al. 2010).

In n6-OHDA-lesioned rats, striatal extraneuronal levels of HO·, reflected by measures of 2,3- and 2,5-DHBA, were elevated ~2- to 3-fold—similar to the higher striatal tissue levels of HO· in these rats. However, acute L-DOPA treatment had no influence on extraneuronal HO· levels (Nowak et al. 2010).

8 Summary on n6-OHDA-Lesioned Rats as a Model for Severe PD

In rats lesioned shortly after birth with 6-OHDA, there is near-total striatal dopaminergic denervation which is maintained throughout the life span. Rat pups do not die from the 6-OHDA treatment and are able to eat, drink, and maintain motor control. Growth rate is only slightly less than that of controls, from which n6-OHDA-lesioned rats are otherwise nearly indistinguishable except by special testing. The destructive effect of n6-OHDA treatment on nigrostriatal dopaminergic nerves is near complete, is reproducible and has a variability of only ~1 %.

The n6-OHDA model of PD fulfills neurochemical criteria of other rodent models of PD, but does not suffer from the debilitating (aphagia, adipsia, paralysis) and oft fatal effects of adulthood bilateral 6-OHDA injections (Ungerstedt 1971a; Kostrzewa et al. 2006). In adulthood, n6-OHDA-lesioned rats have a basal increase in HO·/ROS levels in tissue and in microdialysates (i.e., intracellularly and extracellularly). Also, acute L-DOPA treatment of adulthood n6-OHDA-lesioned rats produces a greater increase in extraneuronal levels of DA, an increase in striatal tissue levels of both DA and DOPAC, and a reduction in striatal tissue HO·. Effects

are analogous to findings in other rodent models of PD. One negative aspect of n6-OHDA-lesioned rats is a risk for L-DOPA induction of self-injurious behavior.

The striatal serotoninergic hyperinnervation in n6-OHDA-lesioned rats represents an effect that is not repeatable with other rodent models, but this element does not appear to alter the expected basal levels relating to DA nor the expected effects of L-DOPA. Also, it would be possible to (1) attenuate the serotoninergic hyperinnervation by administering a fixed dose of the serotoninergic neurotoxin 5,7-DHT simultaneous with n6-OHDA administration (see Brus et al. 1994) or (2) eliminate the serotoninergic hyperinnervation in adulthood by 5,7-DHT treatment (Kostrzewa et al. 1994).

The n6-OHDA-lesioned rat is considered to be a good model of severe PD. Advantages relating to behavioral elements are the maintained ambulation, maintained nutrition, and maintained grooming—such that adult n6-OHDA-lesioned rats are healthy and able to live the full life span, as per intact control rats. Advantages relating to neurochemical status are reflected in the near-total destruction of nigrostriatal fibers and near-total dopaminergic denervation of striatum—akin to the neurochemical status approached in severe PD in humans. The n6-OHDA-lesioned rat displays behavioral activation with acute L-DOPA treatment, and there is a corresponding increase in striatal tissue DA content and increase in extraneuronal DA content. The n6-OHDA-lesioned rat reliably fulfills the criteria for an animal model of severe PD.

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