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Dopamine Receptor Supersensitivity: An Outcome and Index of Neurotoxicity

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The characteristic feature of neurotoxicity is a definable lesion which can account for observed deficits, corresponding to loss of nuclei or axonal fibers normally comprising a specific pathway or tract. However, with ontogenetic lesions, the operative definition fails. In rats lesioned as neonates with 6-hydroxydopamine (6-OHDA), near-total destruction of dopamine- (DA-) containing nerves is produced, and this itself is definable. However, the most prominent feature of rats so-lesioned is the DA receptor supersensitivity (DARSS) that develops and then persists throughout the lifespan. DA D_1 receptors show overt supersensitivity to agonists producing vacuous chewing movements (VCMs), while D_1 receptors associated with locomotor activity have a latent supersensitivity that must be unmasked by repeated D_1 or D_2 agonist treatments — a 'priming' phenomenon. This D_1 DARSS is not usually associated in either a change in D_1 receptor number (B_{max}) or affinity (K_d). In contrast to D_1 DARSS, D_2 receptors are not so predictably supersensitized by a lesion of DA neurons. In reality, the permanently exaggerated response to an agonist by supersensitized receptors is *per se* a manifestation of neurotoxicity. Despite dramatic behavioral responses mediated by supersensitized receptors, DARSS has not been easy to correlate with enhanced production of second messengers or early response genes. Altered signaling (i.e., neuronal cross-talk) in defined pathways may represent the mechanism that produces so-called receptor supersensitization. Long-lived agonist-induced behavioral abnormality, with or without anatomic evidence of a neuronal lesion, is one of the products of DA D_1 receptor supersensitization – itself an index of neurotoxicity.

Keywords: Dopamine; 6-Hydroxydopamine; Neurotoxicity; Receptor supersensitivity; Receptor priming

INTRODUCTION

The selective neurotoxins 6-hydroxydopamine (6-OHDA) and 6-hydroxydopa (6-OHDOPA) are known to produce definitive anatomic and histochemically definable damage to catecholaminergic neurons at any stage of life. However, when the effect occurs during ontogenetic development, prolonged or life-long neuronal reorganization or adaptive change ensues (Breese and Traylor, 1972; Sachs and Jonsson, 1972; Kostrzewa and Harper, 1974). In this report we present evidence to support the contention that the adaptive change of receptors *per se* is a categorization of neurotoxicity. Specifically, we pose DA receptor supersensitivity (DARSS) to be an index of neurotoxicity, with or without evidence of anatomic damage.

NEONATAL 6-OHDA TREATMENT DESTROYS NIGRONEOSTRIATAL DA FIBERS

In the early 1970s, shortly after discovery of 6-OHDA as a neurotoxin, several groups showed that when rats were treated early in postnatal ontogeny with 6-OHDA (>50 μg icv), there was life-long suppression of development of DA content in the neostriatum (Breese and Traylor, 1972; Lytle *et al.*, 1972; Sachs and Jonsson, 1972). This effect was attributable to a reduction in innervation of neostriatum by tyrosine hydroxylase- or DA-immunoreactive fibers (Snyder *et al.*, 1986; Descarries *et al.*, 1992) and was actually due to overt loss of nigroneostriatal DA neurons resulting from destruction of >99% of the 7,000 DA perikarya (per side) in left and right pars compacta substantia nigra (SNpc) (Berger *et al.*, 1985; Fernandes Xavier *et al.*, 1994). Despite the dramatic reduction in numbers of DA fibers innervating neostriatum, a relatively high level of extraneuronal DA is maintained, as the *in vivo* microdialysate level of DA is reduced by 44-88% vs a typical 99% DA decrease in neostriatal tissue

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(Castañeda *et al.*, 1990). See Kostrzewa *et al.* (1998) for a more complete discussion on this theme.

SEROTONIN FIBERS SPROUT IN RESPONSE TO ONTOGENETIC LOSS OF NEOSTRIATAL DA FIBERS

An increase in neostriatal serotonin (5-HT) content develops as a consequence of DA-denervation of neostriatum (Mailman *et al.*, 1983; Breese *et al.*, 1984; Stachowiak *et al.*, 1984), reflecting 5-HT hyperinnervation (Snyder *et al.*, 1986; Luthman *et al.*, 1987; Towle *et al.*, 1989; Descarries *et al.*, 1992). Proliferation of 5-HT fibers occurs slowly, over a period of 2-3 months (Dewar *et al.*, 1990), and only after loss of >80% of DA content of neostriatum (Towle *et al.*, 1989; Gong *et al.*, 1993b) within the first 10 days after birth (Kostrzewa *et al.*, 1993a). The major portion of 5-HT fiber proliferation occurs in rostral vs caudal neostriatum (Molina-Holgado *et al.*, 1994; Soucy *et al.*, 1994; Descarries *et al.*, 1995; Mrini *et al.*, 1995). Presumably, the resting extraneuronal level of 5-HT is similar to normal, as determined from *in vivo* microdialysates (Jackson and Abercrombie, 1992). However, in unpublished studies, we have found that the neostriatal *in vivo* microdialysate level of 5-HT is elevated several-fold in rats lesioned as neonates with 6-OHDA.

DA RECEPTOR NUMBER IS ALTERED BY NEONATAL 6-OHDA TREATMENT

DA D_1 Receptors

The B_{max} and K_d of DA D_1 and D_{1A} receptors were generally found to be unaltered in whole neostrium of adult rats that had been lesioned as neonates by 6-OHDA (Breese *et al.*, 1987; Duncan *et al.*, 1987; Luthman *et al.*, 1990; Hamdi and Kostrzewa, 1991; Duncan *et al.*, 1993). However, in some studies, particularly when rostral neostriatum alone was assessed, DA D_1 receptor number was found to be slightly reduced (Dewar *et al.*, 1990; Gelbard *et al.*, 1990; Radja *et al.*, 1993a,b). By probing with an oligonucleotide for the sequenced and cloned D_1 receptor gene, the level of D_1 receptor mRNA was found to be reduced in such rats (Gong *et al.*, 1994). Therefore, it may be that there is reduced synthesis or enhanced degradation of D_1 receptors in the striatum of adult rats that had been 6-OHDA-lesioned as neonates. When repeated treatments were given with the DA D_1 agonist SKF 38393 HCl [(±)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol, 3 mg/kg per week X 4 weeks), a process known as *receptor priming*, the reduction in D_1 receptor mRNA was eliminated (Gong *et al.*, 1994). It has been suggested that the apparent discrepancy in reports on DA D_1 receptor number in neostriatum of 6-OHDA-lesioned rats may be related to priming (or non priming) of D_1 receptors.

The inhibitory response on neostriatal neuronal firing to the D_1 agonist SKF 38393 was increased in 6-OHDA-lesioned rats (Radja *et al.*, 1993a). Using DA in competition for SCH 23390 [*R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine] binding to neostriatal homogenates *in vitro*, Gong *et al.* (1994) found that that there was no apparent change in the percentage of high-affinity binding sites for D_1 receptors, nor in the binding constant for high affinity DA D_1 receptors (K_H) or low affinity DA D_1 receptors (K_L) in the 6-OHDA-lesioned rats. Also, DA-stimulated cAMP production was not altered (Simson *et al.*, 1992; Gong *et al.*, 1994), nor was basal-, NaF-, nor forskolin-stimulated cAMP production in the striatum of the 6-OHDA-lesioned rats. Futhermore, priming did not affect any of the parameters (Gong *et al.*, 1994).

Although binding constants for D_1 receptors are not substantially altered, nor is second messenger production, neostriatal expression of the immediate early gene *c-fos* is enhanced by SKF 38393 treatment of 6-OHDA-lesioned rats (Johnson *et al.*, 1992; Simson *et al.*, 1992). Therefore, although there are indications of slight biochemical changes in response to D_1 agonists in target cells in the neostriatum of 6-OHDA-lesioned rats, there are no overt changes in D_1 receptor binding characteristics or in second messenger production, indicating that there is no outstanding feature that can be used to account for the phenomenon of D_1 DARSS.

DA D_2 Receptors

In those studies in which the DA D_2 receptor antagonist [^{3}H]spiperone was used as a radioligand for D_2 receptors, the B_{max} and K_d were found to be unaltered in homogenates of neostriatum of 6-OHDA-lesioned rats (Breese *et al.*, 1987; Duncan *et al.*, 1987; Kostrzewa and Brus, 1991; Kostrzewa and Hamdi, 1991). However, when the radioligand [^{3}H]raclopride was used, a 30-40% increase in the B_{max} for D_2 receptors was found in the neostriatum of such rats (Dewar *et al.*, 1990; Radja *et al.*, 1993a). In this case, there was no accompanying change in the mRNA for D_2 receptors (Chen and Weiss, 1991; Radja *et al.*, 1993a), nor in firing rate of neostriatal neurons in response to an iontophoretically applied D_2 agonist (Radja *et al.*, 1993a).

Breese and others have shown that D_2 DARSS is pro-

duced to some extent in rats lesioned as neonates with 6-OHDA (Breese *et al.*, 1985a, 1985b, Criswell *et al.*, 1989; Kostrzewa *et al.*, 1990). However, behavioral effects are not so prominent in these rats after D_2 agonist treatment, as contrasted with D_1 agonist treatment.

In a related series of studies in intact rats (i.e., non-lesioned rats) we showed that D_2 DARSS can be produced by repeated treatments with the D_2 agonist quinpirole (i.e., a receptor priming process), so that such rats in adulthood showed enhanced quinpirole-induced yawning (Kostrzewa and Brus, 1991), antinociception (Kostrzewa et al, 1991), stereotyped behaviors such as vertical jumping (Kostrzewa *et al.*, 1990; Kostrzewa *et al.*, 1993c), and spacial memory deficits with enhanced skilled reaching in adulthood (Brown *et al.*, 2002). Robust quinpirole-priming can be produced by extremely low doses of quinpirole (50 μg/kg per day) and for short periods of treatment (i.e., P0-P11, or P12-P22, or P22-P33) (Kostrzewa *et al.*, 1993b). Similar priming can even be produced by repeated quinpirole treatments in adulthood, where numbers of doses and not dosage is seemingly the important criterion (Szechtman *et al.*, 1994).

In non-lesioned rats that were quinpirole-primed as neonates (quinpirole HCl, 50 μg/kg per day for the first 11 days from birth), we found that a single treatment with amphetamine (1.0 mg/kg) produced a five-fold greater release of DA into the *in vivo* microdialysate, vs. levels in control rats (Nowak *et al.*, 2001). Such an effect is believed to represent a subsensitization of DA D_2 autoreceptors on nigral or ventral tegmental neurons – reflecting less negative feedback inhibition by DA. Quinpirole selectivity for this sensitization was demonstrated by the failure of the largely D_3 agonist 7-OHDPAT to replicate these effects of quinpirole (Oświecimska *et al.*, 2000).

Similar D_2 receptor sensitization is produced by a neonatal lesion of 5-HT fibers with 5,7-dihydroxytryptamine (Brus *et al.*, 1995). It now appears that many of the behavioral alterations found in rats neonatally lesioned with 6-OHDA, can be explained by altered D_2 receptor sensitivity (Kostrzewa, 1995).

5-HT RECEPTOR NUMBER IS ALTERED BY NEONATAL 6-OHDA TREATMENT

In the neostriatum of adult rats that had been lesioned as neonates with 6-OHDA, there was a 30% increase in neostriatal 5-HT_{1B} receptors, 40% increase in 5-HT_{1nonAB} (i.e., 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{2C} receptors), and 60% increase in 5-HT_2 receptors (Radja *et al.*, 1993a). Also, the inhibitory response to iontophoretic application of the 5-$HT_{1B/2C}$ agonist *m*-chlorophenylpiperazine (*m*-CPP) in neostriatum was significantly increased in 6-OHDA-lesioned rats (El Mansari *et al.*, 1994). These findings demonstrate the multiplicity of changes in the 5-HT receptor phenotypy in neostriatum of rats lesioned as neonates with 6-OHDA.

LATENT SUPERSENSITIVITY OF DA D_1 RECEPTORS IS UNMASKED BY D_1 AGONIST PRIMING

In rats lesioned as neonates with 6-OHDA, the first dose of SKF 38393 in adulthood produced effects similar to those observed after SKF 38393 treatment of intact rats. However, when SKF 38393 was administered at weekly intervals, the stereotyped and locomotor effects produced by L-DOPA, SKF 38393, or apomorphine became greatly enhanced. Also, all subsequent treatments by these agents, throughout the remaining lifespan, gave similarly exaggerated effects. Accordingly, these DA D_1 receptors were said to be supersensitized (Breese *et al.*, 1984; 1985a,b; 1987), while the gradual induction of supersensitivity by repeated agonist treatments was characterized as a *priming* process. Locomotor effects appeared to be mediated by D_1 receptors in nucleus accumbens, while stereotyped effects appeared to be mediated by D_1 receptors in either nucleus accumbens or neostriatum (Breese *et al.*, 1987). Moreover, D_1 receptors could be primed by either repeated D_1 agonist treatments (homologous priming) or repeated D_2 agonist treatments (heterologous priming) (Criswell *et al.*, 1989).

If administered at daily intervals during postnatal ontogeny, SKF 38393 could partially prime D_1 receptors, and additional SKF 38393 treatments in adulthood produced still-greater DARSS (Hamdi and Kostrzewa, 1991; Gong *et al.*, 1993a).

OVERT SUPERSENSITIVITY OF DA D_1 RECEPTORS IN 6-OHDA-LESIONED RATS

In rats lesioned as neonates with 6-OHDA, the first treatment in adulthood with a low dose of SKF 38393 produced an increase in the number of vacuous chewing movements (VCMs), as compared to the effect in intact rats (Kostrzewa and Gong, 1991; Kostrzewa and Hamdi, 1991; Gong *et al.*, 1992). This effect was dose-dependent, and was mediated by a dose of SKF 38393 that was 30-fold lower than the requisite dose in intact rats. It appears that DA must be depleted in neostriatum by >97% (Gong *et al.*, 1993b) and within the first 3 days for

enhancement of SKF 38393 effects (Kostrzewa *et al.*, 1993a). DA D_1 receptor sensitization apparently is mediated by nitric oxice (NO), as the NO synthase inhibitor nitro-L-arginine attenuated SKF 38393-induced oral activity in neonatal 6-hydroxydopamine-lesioned rats (Brus *et al.*, 1997; Kasperska *et al.*, 1999).

OVERT SUPERSENSITIVITY OF 5-HT RECEPTORS IN 6-OHDA-LESIONED RATS

In rats lesioned as neonates with 6-OHDA, the first treatment in adulthood with a low dose of *m*-CPP (5-$HT_{1B/2C}$ agonist) produced VCMs, quantitatively greater than that produced by DA D_1 agonist treatment (Gong and Kostrzewa, 1992; Kostrzewa *et al.*, 1999). However, this effect is not directly related to the magnitude of the lesion of DA fibers or the extent of sprouting by 5-HT fibers (Kostrzewa *et al.*, 1996). Rather, 5-HT receptor sensitization was produced if striatal DA was reduced by >97% with striatal 5-HT content elevated by >50% (Gong *et al.*, 1993b), and when the DA lesion was produced within the first 10 days after birth (Kostrzewa *et al.*, 1993a). Although the enhanced *m*-CPP effect could be attenuated by the 5-HT_2 blocker mianserin (Gong *et al.*, 1992), the *m*-CPP effect was not attenuated by a DA D_1 receptor antagonist (Gong *et al.*, 1992). Moreover, even if administered directly into the dorsal striatum, mianserin effectively blocked effects of both DA D_1 and 5-HT_2 agonists (Plech *et al.*, 1995). Therefore, 5-HT receptor sensitization is independent of DA receptor sensitization. This is further supported by the finding that a neonatal 5,7-DHT lesion of rats resulted in the production of 5-HT receptor sensitization in the absence of DA D_1 receptor sensitization (Brus *et al.*, 1994). However, in rats lesioned neonatally with 5,7-DHT alone, there was enhanced sensitization of DA D_2 receptors (Brus *et al.*, 1995), indicating the importance of 5-HT neurons in regulating both DA D_1 and DA D_2 receptors.

5-HT NEURONAL MEDIATION AND PRESERVATION OF DA D_1 RECEPTOR SUPERSENSITIVITY

The DA D_1 receptor antagonist SCH 23390 failed to alter the magnitude of effect of *m*-CPP on vacuous chewing in 6-OHDA-lesioned rats. However, the 5-$HT_{1B/2C}$ antagonist mianserin effectively attenuated both *m*-CPP-induced and SKF 38393-induced vacuous chewing (Gong *et al.*, 1992), even if both substances were administered directly into the striatum (Plech *et al.*, 1995). Blockers of 5-HT_{1A}, 5-HT_{2A}, and 5-HT_3 receptors had no effect on *m*-CPP-induced vacuous chewing (Gong *et al.*, 1992). Although 5-HT receptor sensitization occurs in the absence of D_1 receptor sensitization, D_1 receptor sensitization has not been observed in the absence of 5-HT receptor sensitization. Therefore, it appears that DA D_1 receptor supersensitivity is mediated specifically by supersensitized 5-$HT_{1B/2C}$ receptors (Gong *et al.*, 1992; Kostrzewa *et al.*, 1992).

If rats are treated as neonates with both 6-OHDA and 5,7-dihydroxytryptamine (5,7-DHT), to respectively lesion DA and 5-HT fiber innervation of neostriatum, SKF 38393 fails to produce increased numbers of VCMs in rats (Brus *et al.*, 1994). If rats previously lesioned as neonates with 6-OHDA are lesioned in adulthood with 5,7-DHT, D_1 receptor sensitization is similarly suppressed (Brus *et al.*, 1994).

CLINICAL RELEVANCE OF 5-HT-MEDIATION OF DA RECEPTOR SUPERSENSITIVITY

Rats lesioned as neontates with 6-OHDA have been proposed as a suitable animal model of Lesch-Nyhan syndrome in humans (Breese *et al.*, 1990). Recently, Allen and Davis (1999) showed that both SKF 38393 (D_1 receptor agonit) and *m*-CPP (5-$HT_{1B/2C}$ receptor agonist) would evoke self-biting and self-mutilation in such rats. Although SCH 23390 effectively blocked SKF 38393-induced effects, it was ineffective against *m*-CPP. However, both SKF 38393 and *m*-CPP-induced effects were blocked by either the 5-$HT_{1B/2C}$ antagonist mianserin or by a 5,7-DHT partial lesion of 5-HT neurons. Findings implicate 5-HT receptor antagonists as a putative therapy towards abating self-injurious behavior in Lesch-Nyhan patients.

Rats lesioned as neonates with 6-OHDA and subsequently lesioned as adults with 5,7-DHT, display spontaneous hyperlocomotor activity that is attenuated by low-dose amphetamine (Kostrzewa *et al.*, 1994) These rats have been posed as an animal model for hyperactivity disorder; and have been shown to be responsive to 5-HT receptor antagonists (unpublished).

Rats treated continuously, for several months, with haloperidol represent a reasonable animal model of tardive dyskinesia (TD) (Gunne *et al.*, 1986; Mithani *et al.*, 1987; Tamminga *et al.*, 1990). In rats so-treated, spontaneous vacuous chewing develops and persists as long as haloperidol continues to be administered. It has now been shown that numbers of haloperidol-induced VCMs can be dramatically increased in rats lesioned as neonates with 6-OHDA; that in such rats, VCMs persist for at least 8 months even after discontinuing haloperidol treatment; and that VCMs are unrelated to changes in DA D_2

receptor number (i.e., B_{max}). It has also been shown that spontaneous VCMs in the 6-OHDA-lesioned rats are reversed not by the D_1 antagonist SCH 23390, but by the 5-$HT_{1B/2C}$ antagonists mianserin or mesulergine (Kostrzewa and Huang, 1997). Thus, there now is a means to model haloperidol-withdrawn TD (Huang *et al.*, 1997); and there is evidence implicating 5-$HT_{1B/2C}$ antagonists as putative drugs for TD, which had been viewed in the past as a disorder of DA receptor supersensitivity.

Quinpirole-primed rats display compulsive checking, and rats so-treated have been proposed as a model of obsessive compulsive disorder (Szechtman *et al.*, 1998) and its treatment with nicotine (Tizabi *et al.*, 2002), which reverses some of the exaggerated behaviors in rats (Tizabi *et al.*, 1999).

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