Noradrenergic–Dopaminergic Interactions Due to DSP-4–MPTP Neurotoxin Treatments: Iron Connection

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Abstract The investigations of noradrenergic lesions and dopaminergic lesions have established particular profiles of functional deficits and accompanying alterations of biomarkers in brain regions and circuits. In the present account, the focus of these lesions is directed toward the effects upon dopaminergic neurotransmission and expression that are associated with the movement disorders and psychosis-like behavior. In this context, it was established that noradrenergic denervation, through administration of the selective noradrenaline (NA) neurotoxin, DSP-4, should be performed prior to the depletion of dopamine (DA) with the selective neurotoxin, MPTP. Employing this regime, it was shown that (i) following DSP-4 (50 mg/kg) pretreatment of C57/Bl6 mice, both the functional and neurochemical (DA loss) effects of MPTP (2 × 20 and 2 × 40 mg/kg) were markedly exacerbated, and (ii) following postnatal iron (Fe^{2+}, 7.5 mg/kg, on postnatal days 19–12), pretreatment with DSP-4 followed by the lower 2 × 20 mg/kg MPTP dose induced even greater losses of motor behavior and striatal DA. As yet, the combination of NA-DA depletions, and even more so Fe^{2+}–NA-DA depletion, has been considered to present a movement disorder aspect although studies exploring cognitive domains are lacking. With intrusion of iron overload into this formula, the likelihood of neuropsychiatric disorder, as well, unfolds.

Keywords NA-DA denervations · Mice · DSP-4 · MPTP · Function · Biomarkers · Deficits · Iron overload

Contents

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On the basis of neuropathological evidence, central noradrenaline (NA) system impairments have been linked to various neurodegenerative disorders including parkinsonism and other movement disorders (Alvord and Forno 1992). For example, in Parkinson's disease (PD) patients' postmortem neurochemical analyses have confirmed huge losses of NA together with the dopamine (DA) depletions (Hornykiewizc and Kish 1987). In analyses of thalamic neuronal discharge patterns, it was indicated that in PD patients NA was severely reduced in the motor thalamus and also in other regions of the thalamus (Pifl et al. 2012). Furthermore, Pifl et al. (2013) analyzed NA, DA, and serotonin (5-HT) in the motor (ventrolateral and ventroanterior) and non-motor (mediodorsal, centromedian, ventroposterior lateral and reticular) thalamic nuclei of MPTP-treated monkeys that had been found to be (i) constantly asymptomatic; (ii) who had recovered from mild parkinsonism; and (iii) animals presenting either with stable, moderate, or severe parkinsonism. They observed that only the symptomatic parkinsonian animals showed significant losses of NA specifically in the motor thalamus, with the ventroanterior motor nucleus being affected only in the severe parkinsonian animals. Contrastingly, the striatal DA loss was identical in both the mild and severe symptom groups. Certainly, all three neurotransmitters, NA, DA, and 5-HT, were reduced significantly in the rostro-caudal regions of the hypothalamus of patients with idiopathic PD (Shannak et al. 1994). The putatively protective role of noradrenergic innervation for DA neurons was implied from a postmortem study of 20 brain areas, dopamine loss in PD was negatively, but strongly, correlated with healthy NA levels, with regions rich in NA (e.g., the noradrenaline-rich portion of the nucleus accumbens) spared from dopamine loss (Tong et al. 2007).

1 DSP-4 Lesioning of NA

The selective NA neuron denervating effects of DSP4 (*N*-[2-chloroethyl]-*N*-ethyl-2-bromobenzylamine) within several brain regions, including the forebrain, midbrain, cerebellum, brain stem, and spinal, accompanied alterations in biomarkers and functional parameters have been documented prodigiously (Archer and Fredriksson 2000, 2001; Archer et al. 1982, 1983, 1984a, b, 1986a; Dooley et al. 1983a; Fredriksson and Archer 2000; Jonsson and Hallman 1982; Jonsson et al. 1981, 1982; Hallman and Jonsson 1984; Hallman et al. 1984; Ponzio et al. 1981; Ross 1976; Ross and Renyi 1976; Sundström et al. 1987). Consistently, brain tissue levels of NA are decreased to between 10 and 30 % of control values (Ross and Stenfors 2015). Systemic administration of DSP4 (50 mg/kg and upwards, i.p. or s.c. injections, generally two weeks before testing) induced marked and long-lasting reductions of dopamine β-hydroxylase activity (Archer et al. 1984a, b, 1985; Ross 1976; Ross and Renyi 1976). Profound and permanent depletions of endogenous NA have been obtained repeatedly in several brain regions, such as the cerebral and cerebellar cortex, hippocampus and spinal cord, generally leaving dopamine (DA) and 5-hydroxytryptamine (5-HT) neurons largely intact;

nevertheless, pretreatment with the 5-HT reuptake inhibitor, zimelidine, unfailingly leaves 5-HT neurons intact (Archer 1982; Archer and Fredriksson 2001; Archer et al. 1984a, b, 1986b; Liu et al. 2015a, b; Rényi et al. 1986). Any transient peripheral tissue depletions that may have appeared following the 50 mg/kg dose of DSP-4 (e.g., Archer et al. 1982; Liang et al. 1995) disappeared within 10 days.

Systemic administration of DSP-4 has been shown to cause minor losses of cortical 5-HT, although not always so, in rats and mice (e.g., Archer et al. 1984a, b, 1985; Roczniak et al. 2013, 2015). Invariably, it was demonstrated that pretreatment with 5-HT reuptake inhibitors, whether zimelidine (20 mg/kg) or fluoxetine (20 mg/kg), up to 30 min before DSP-4 administration, prevented any loss of 5-HT, without affecting the extent of NA denervation (Archer et al. 1986b; Bello et al. 2014; Dabrowska et al. 2008; Fowler et al. 1988; Heal et al. 1993; Post et al. 1987). Functional analyses applying receptor ligand agonists of the DA and 5-HT systems have demonstrated that these neurotransmitter pathways were not changed in DSP-4 rats (Dooley et al. 1983b); neither did the systemic DSP-4 administration produce any notable effects upon the normal functioning of the hypothalamic–pituitary–adrenal axis (Bugajski et al. 1995). Nevertheless, in a study of stress-sensitive and genetic factors underlying dependence behavior in Sprague–Dawley and Wistar–Kyoto rats, Fox et al. (2015) using DSP-4 to deplete NA selectively in these strains showed that DSP-4-treated Sprague–Dawley rats demonstrated a dependence-like phenotype, whereas the DSP-4-treated Wistar–Kyoto rats were unchanged. A comprehensive analysis of the neurotoxic actions of DSP-4 that evaluated different patterns of monoamine-producing depletions over various brain regions in different strains of rats and mice from 3 to 14 days after neurotoxin injections has been described (Fornai et al. 1996, 1997; Hurko et al. 2010; Kostrzewa 2009; Kostrzewa et al. 2011; Nowak et al. 2009). With regard to the possible, transient yet small depletions of 5-HT, following DSP-4, both strain and species differences have been described that pertain to various due to use of the same dose of neurotoxin in different strains/species (Aulakh et al. 1992; Fornai et al. 1996, 2001). Long-term pretreatment of rats with DSP-4 induced marked supersensitivity to noradrenergic (Archer and Fredriksson 2000) and cross-sensitivity to opiate (Archer and Fredriksson 2001).

2 MPTP-Lesioning of DA

The selective DA neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), has been shown regularly to induce parkinsonism in human and non-human primates (Langston 1985), that resulted in the loss of substantia nigra cells in the pars compacta of adult humans/adults (Bubak et al. 2015; Mathai et al. 2015; Uehara et al. 2015). Systemic administration of MPTP to C57/Bl6 mice, generally at a dose of 2 × 40 mg/kg, s.c., invariably induced hypokinesia, reflected by loss of locomotion, rearing and total activity in standardized activity test chambers, that could be reversed with a 20 mg/kg dose of l-dopa (Fredriksson et al.

1990; Sundström et al. 1990), accompanied by an 85–90, or more, % loss of DA (Bhargava and Perlow 1988; Schultz et al. 1985; Zuddas et al. 1992). Less rigorous dose regimes, e.g., 2 × 20, or 25, or 30 mg/kg of the neurotoxin, have been less effective in inducing hypoactivity although DA concentrations may indicate up to 50–80 % reductions (Giovanni et al. 1994a, b; Heikkila et al. 1989; Sonsalla and Heikkila 1986). Reductions in 5-HT levels are observed in midbrain and hippocampus regions only in acute and subacute MPTP-treated-mice (Pain et al. 2013). The parameters of MPTP neurotoxicity are virtually permanent (up to and beyond 52 weeks after treatment) with marked correlations between the functional deficits, particularly hypoactivity (locomotion), the neurochemical (DA) levels, severe depletions of DA and metabolites (but see Date et al. 1990), and a dose- and time-dependent recovery of several parameters of motor behavior following the administration of l-dopa, the DA precursor (Archer and Fredriksson 2003; Fredriksson and Archer 1994; Fredriksson et al. 1999; Goshima et al. 1991; Jonsson et al. 1985; Youdim and Arraf 2004). Postnatal iron administration (Fe^{2+}, on postnatal day, at doses of 7.5 or 15 mg/kg) exacerbated the functional, hypokinesia, and neurochemical, DA, deficits that were caused by both the lower (2 × 20 mg/kg) and the higher (2 × 40 mg/kg) dose regimes of MPTP, as well as applying other iron–MPTP combinations (Ayton et al. 2014; Fredriksson and Archer 2003; Fredriksson et al. 2001; Hare et al. 2013; You et al. 2015).

In an MPTP-lesioned primate model, apathy scores were elevated following MPTP, and these scores correlated with PET-scan measures of dopaminergic terminals in the dorsal lateral prefrontal cortex, ventromedial prefrontal cortex, and insular cortex of the treated animals (Tian et al. 2015), implicating dopaminergic dysfunction within the ventral tegmental area-insular cortex pathway plays a role in the manifestation of apathetic behaviors, possibly affecting motor activity. Using a type of 'staging' (Archer et al. 2011) to illustrate parkinsonian state (naive, mild, moderate, and severe) and recording the spontaneous local field potentials were recorded throughout the sensorimotor globus pallidus. Connolly et al. (2015) have described a novel mechanistic framework to understand how progressive loss of dopamine translates into abnormal information processing in the pallidum through alterations in oscillatory activity. Liu et al. (2015a, b) have presented a highly progressive model of parkinsonism in the cynomolgus monkey, a primate, through giving intravenous injections of MPTP (0.2 mg/kg) over 15 days; this procedure induced a stable parkinsonism development over 90 days, at which point the symptoms were stable. Noninvasive positron emission tomographic neuroimaging of vesicular monoamine transporter 2 with 9-[(18)F] fluoropropyl-(+)-dihydrotetrabenazine ([(18)F]AV-133) displayed evidence of the progressive loss of striatal uptake of [(18)F]AV-133. The dopaminergic denervation severity showed a significant linear correlation with the clinical rating scores and the bradykinesia subscores. The progressive feature of MPTP-induced parkinsonism is an important current aspect of MPTP-induced deficits (Archer and Fredriksson 2013; Blesa et al. 2010; Nagai et al. 2012).

3 NA-DA Lesions and Iron Overload

Following the early demonstration of NA-DA neuron interactions (Persson and Waldeck 1970), the requirement for intact noradrenergic pathways for dopaminergic functioning has been studied (Andén and Grabowska 1976; Dolphin et al. 1976a, b; Kostowski 1979; O'Donohue et al. 1979; Tassin et al. 1992). In a primate study, it was shown that denervation of NA pathways following insult to the locus coeruleus exacerbated the neurotoxic damage leading to the experimental parkinsonism following administration of MPTP (Bing et al. 1994). Using subtoxic doses of MPTP into unilateral locus coeruleus 6-hydroxydopamine (6-OHDA) lesions in mice, it was observed there was a significant loss of dopaminergic cells only found in the substantia nigra on the side of the locus coeruleus lesions (Bing et al. 1994). Following DSP-4-induced losses of NA exceeding 75 % in brain regions, the concentrations of endogenous DA in microdialysates from the caudate nucleus and nucleus accumbens were reduced by 52 and 28 %, respectively (Lategan et al. 1992). Similarly, the pretreatment of mice with DSP-4 (40 mg/kg) exacerbated striatal DA loss following MPTP (4 × 10 mg/kg) by a factor of 60 %, whereas by itself DSP-4 did not affect striatal DA (Marien et al. 1993). It should be noted that these doses of the neurotoxins were essentially lower that those applied in the studies above (e.g., Archer et al. 1982; Fredriksson and Archer 1994) and therefore rather impressive. Fornai et al. (1997) measured the acute effects of MPTP on the nigrostriatal DA pathway in DSP-4 lesioned C57/6N mice that were compared to non-NA-lesioned mice that received only MPTP. They obtained a more marked acute DA depletion persisting at 12 h in DSP-4 + MPTP mice compared to MPTP only mice. It appears that in the absence of locus coeruleus axons a more pronounced sensitivity, or 'supersensitivity,' possibly to the loss of a 'recovery-capacity' after noradrenergic denervation (Goldstein 2006), in the striatal DA neurons is produced. Nevertheless, despite successful lesioning of both noradrenergic and dopaminergic neurons in rat brains, no changes in catechol-O-methyltransferase (COMT) protein expression or activity were obtained implying that COMT is not present in DA and NA neurons (Schendzielorz et al. 2013).

Several of the studies described above (e.g., Fornai et al. 1997) applied a neurotoxin dose regime that involved acute administrations. The procedure employed by (Nishii et al. 1991) may be termed 'semi-acute.' They treated 7-week-old C57 black mice as follows, in four groups: Group (i) MPTP (30 mg/kg) was administered each day over 10 days; Group (ii) MPTP treatment as for Group (i), + DSP-4 (50 mg/kg) administered on the final (10th) day of MPTP treatment; Group (iii) vehicle administered over 10 days and DSP-4 (50 mg/kg) on the 10th day (as for Group (ii); and Group (iv) vehicle administered over consecutive days 10 days. They then measured spontaneous and l-dopa-induced motor activity over the next 7–10 days. They obtained a marked reduction in spontaneous motor activity during the initial period (1–2 days) following cessation of neurotoxin treatments which had disappeared 7–10 days later. However, the administration of l-dopa (200 mg/kg) combined with DCI (25 mg/kg) induced a marked rise in the motor activity of the

Group (i) mice, treated with MPTP over 10 days; this peak of motor activity was severely attenuated in the Group (ii) mice, treated with MPTP (10 days) then DSP-4 (Day 10), as expressed by a lower peak effect (35 % less) and lesser peak duration (60 %). Striatal loss of DA was quite comparable in the (i) MPTP, and (ii) MPTP + DSP-4 groups, 82 and 85 %, respectively, which is hardly an exacerbating effect of the NA neurotoxin. In the case of the Marien et al. (1993) study, DA loss after MPTP (4 × 10 mg/kg) was 40 % 7 days postneurotoxin and after DSP-4 (40 mg/kg) prior to MPTP was 60 %. As indicated Fornai et al. (1997), the most severe DA losses occurred when DSP-4 was administered before MPTP.

In order to ensure complete recovery from DSP-4, C57/Bl6 mice were not administered MPTP until three weeks later, and the testing of motor activity was not initiated until a further three weeks had passed (Archer and Fredriksson 2006). Thus, three groups of mice were injected DSP-4 (50 mg/kg, 30 min after zimelidine, 20 mg/kg to protect 5-HT neurons) and three groups injected saline. Three weeks later, one DSP-4 group and one saline group were injected a high dose of DSP4 (2 × 40 mg/kg), one DSP-4 group and one saline group were injected a low dose of DSP4 (2 × 20 mg/kg), and one DSP-4 group and one saline group were injected saline. During the spontaneous motor activity tests three weeks, the following was observed: The spontaneous motor activity of the saline–MPTP-treated mice was reduced in a dose-dependent manner, whereas in the DSP-4–MPTP-treated mice was virtually abolished during the 1st 20-min test period and very nearly so during the 2nd 20-min period of testing. Following a suprathreshold 20 mg/kg dose of l-dopa, motor activity was reinstated completely in the saline–MPTP-treated mice but remained markedly reduced in the DSP-4–MPTP-treated mice. Table 1 presents the locomotor and rearing performance of the saline–MPTP-low, saline–MPTP-high, DSP-4–saline, DSP-4–MPTP-low, and DSP-4–MPTP-high expressed as a percentage of the saline–saline group during the 1st 20-min period of testing as well as the percent striatal DA (of saline–saline controls)

Table 1 Locomotion, rearing and striatal DA, as well as l-dopa-induced activity expressed as a percentage of the saline–saline control group by the groups of mice administered either DSP-4 or saline followed three weeks later by either MPTP, low or high dose, or saline (cf. Archer and Frerdiksson 2006)

Spon. activity	Saline–MPTPL (%)	Saline–MPTPH (%)	DSP-4–Saline (%)	[a]DSP-4–MPTPL (%)	[a]DSP-4–MPTPH (%)
Locomotion	27	10	99	4	0.02
Rearing	44	25	98	1	>0.02
Striatal DA	51	13	101	28	5
Saline–MPTPL (%)	Saline–MPTPH (%)	DSP-4–Saline (%)	[a]DSP-4–MPTPL (%)	[a]DSP-4–MPTPH (%)	Saline–MPTPL (%)
Locomotion	89	79	101	43	20
Rearing	89	87	101	84	37

[a]MPTPL = low-dose (20 mg/kg) MPTP; [a]MPTPH = high-dose (40 mg/kg) MPTP

of the same groups. Locomotor and rearing performance, over 360 min, by the same groups following l-dopa (20 mg/kg) is shown also.

These results indicate a severe exacerbation of the MPTP-induced functional and neurochemical deficits following prior administration of DSP-4, i.e., the noradrenergic system denervation. It is evident also that the restorative effects of suprathreshold l-dopa are compromised. In a further pursuance of these DSP-4 pretreatment–MPTP-induced 'ultra-deficits' in DA functional and neurochemical parameters, postnatal iron administration (Fe^{2+}, 7.5 mg/kg, on postnatal days 10–12) was used to induce further the vulnerability of DA neurons. In this study, only the low (20 mg/kg) dose of MPTP was applied (Fredriksson and Archer 2007). Postnatal iron administration further exacerbated all the deficits induced by DSP-4 and MPTP condition. For example, in mice administered MPTP(Low) locomotion was reduced from 25 % of saline–saline control group in the non-iron condition [compare with 27 % in the Archer and Fredriksson study] to 10 % in the iron condition, whereas in the mice administered DSP-4 + MPTP (low) locomotion was reduced from 10 % in the non-iron condition [compare with 5 % in the Archer and Fredriksson study] to 0 % in the iron condition. Similarly, striatal DA concentrations were compromised drastically through the postnatal iron treatment: in the MPTP (low) group, DA was reduced from 52 % in the non-iron condition [compare with 51 % in the Archer and Fredriksson study] to 39 % in the iron condition, whereas in the DSP-4 + MPTP (low) groups DA was reduced from 25 % in the non-iron condition [compare with 28 % in the Archer and Fredriksson study] to 11 % in the iron condition. Postnatal iron administration induced enduring high levels of total iron content of the basal ganglia in all the groups administered postnatal iron following sacrifice and analysis at 100 days-of-age. Nevertheless, the concentration was highest, significantly, in the DSP-4 + MPTP group implying that the combination of these neurotoxins affected brain iron retention. Finally, the co-administration of clonidine (1 mg/kg) with subthreshold l-dopa (5 mg/kg) alleviated the motor deficits of MPTP-treated mice, but pretreatment with DSP-4 reduced markedly the ameliorative effects of clonidine, the α-adrenoceptor agonist (Archer and Fredriksson 2007; Fredriksson and Archer 2007). It has been shown comprehensively that iron overload contributes to the development of neurodegenerative progressions and the acceleration of normal rates of apoptosis primarily due to its participation in the Fenton reaction and production of reactive oxygen species, as well as functional measures in both motor and cognition domains (Fagherazzi et al. 2012; Lavich et al. 2015; Silva et al. 2012). Postnatal iron administration, by itself, induces long-lasting changes in brain function, e.g., transient hypoactivity in activity cages followed hyperactivity and cognitive deficits (de Lima et al. 2007; Fredriksson and Archer 2006). The hyperactivity was exacerbated by apomorphine and abolished by haloperidol (Fredriksson and Archer 2006). The full implications of the balancing role of iron in conditions of loss of DA-NA integrity have yet to be explored and described; nevertheless, the implications of the observations so far offer a neurodegenerative scenario that may be of utility in understanding developmental trajectories of subnormal dimensions.

Loss of integrity, or a 'masked' vulnerability, by DA neurons, and possibly also NA neurons, through postnatal iron overload may well impart an adverse epigenetic condition to the detriment of normal development. Nevertheless, NA neurons in the locus coeruleus appear to be less susceptible to the effects of iron overload than DA neurons in the substantia nigra (Zecca et al. 2004). Dornelles et al. (2010) have shown that transferrin receptor, H-ferritin, and IRP2 mRNA expressions were affected differentially through the aging process and by postnatal iron supplementation in the cortex, hippocampus, and striatum of rats. The epigenetic reprograming of cortical neurons through alterations of dopaminergic circuits (Brami-Cherrier et al. 2014), such as that produced by neurotoxin insults or iron overload, may exert both neurologic and psychiatric expressions of abnormal function as a basis of brain disorder. Finally, Shin et al. (2014), in a rat model of PD, found that NA depletion did not enhance the extent of DA depletion or the loss of tyrosine hydroxylase-positive innervation in the striatum but rather that damage to brainstem NA innervation accelerated development of motor impairments and the onset of l-dopa-induced dyskinesias in 6-OHDA-lesioned (DA-depleted) rats. These observations are reinforced by the finding that additional noradrenergic depletion (in addition to DA depletion) aggravated forelimb akinesia and abnormal subthalamic nucleus activity in the DSP4-6-OHDA rat model of PD (Wang et al. 2014; see also Lindgren et al. 2014).

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