Long-Lived Dopamine D_2-Receptor Supersensitivity: Neurotoxicity in the Presence and Absence of Neuronal Damage

Richard M. Kostrzewa and Russell W. Brown

Contents

Abstract

Overt destruction of a nerve by a highly selective neurotoxin produces an accompanying loss of function. However, the abnormality of nerve loss is broadened by the adaptations of the nerve network with which the damaged nerve would interact.

R. M. Kostrzewa (✉)
Department of Biomedical Sciences, Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA
e-mail: kostrzew@etsu.edu; kostrzew@mail.etsu.edu

R. W. Brown
Department of Biomedical Sciences, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA
e-mail: brown1@etsu.edu

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Further, the resulting absence of synaptic inputs to a receptor field gives rise to a receptor adaptation that adds to the original nerve loss and the adaptations by normally-interactive nerve networks. The focus of the current report is on this latter element – the adaptations of receptor fields in relation to the loss of a nerve. Emphasis is on the monoaminergic nerves, injured in early postnatal ontogeny: dopaminergic and serotoninergic nerves, but mainly dwelling on their respective receptor subtypes. It is the process of long-lived receptor supersensitivity that arises when the respective dopaminergic or serotoninergic nerves are destroyed. The concept of neurotoxicity in the absence of overt neuropathology is highlighted, as this process has been a focus for the past 30 years. Repeated treatments with the dopamine D_2-receptor agonist evokes a permanent development of D_2-receptor supersensitivity even in the absence of nerve damage. DA-R and 5-HT-R sensitization as an expression of neurotoxicity is thus considered and an identifiable neurotoxic event.

Keywords

Dopamine · D_1-Receptor · D_2-Receptor · D_3-Receptor · Norepinephrine · Serotonin · Supersensitivity

Abbreviations

5,7-DHT	5,7-Dihydroxytryptamine
5-HT	5-Hydroxytryptamine, Serotonin
6-OHDA	6-Hydroxydopamine
7-OH-DPAT	(±)-2-(dipropylamine)-7-hydroxy-1,2,3,4-tetrahydronaphthalene
D_1-R	Dopamine D_1-receptor
D_2-R	Dopamine D_2-receptor
D_3-R	Dopamine D_3-receptor
DA	Dopamine
DARSS	Dopamine receptor supersensitivity
RSS	Receptor supersensitivity

1 Introduction

Starting within the 1960s and to the present, a myriad of highly-selective neurotoxins have been discovered. These neurotoxins find use in experimental neuroscience, to uncover mechanisms of neuronal intracellular processes as well as in recognizing the interplay and interactions with neural networks in regulating physiological functions. The status of a neurotoxin is that it is a substance that produces destructive actions on specific neurons. As the field of neuroscience, and with a focus on neurotoxicity, the current theme of the present paper is on the production of "neurotoxicity" by a substance that produces life-altering effects without evidence of an overt neuropathological event.

Beginning with a series of studies beginning in the late 1980s there was recognition that repeated treatments with the relatively selective dopamine (DA) D_2-receptor (D_2-R) agonist quinpirole would sensitize the D_2-R. Significantly, this receptor supersensitization appeared to be life-long, and was associated with the

production of exaggerated behavioral effects. The abnormality is akin to neurotoxicity.

The process of receptor supersensitivity can arise after (a) destruction of dopaminergic neurons and (b) serotoninergic neurons. This relates to (c) DA-Rs, (d) serotonin receptors (5-hydroxytryptamine-R, 5-HT-R), (e) cholinergic/muscarinic-R, or (f) receptors for other neuronal phenotypes. The schema, below, elaborates on DA-R supersensitivity, 5-HT-R supersensitivity – outcomes of overt neuropathology to dopaminergic neural systems and serotoninergic neural systems; and to the outcome of repeated D_2 agonist treatments to evoke D_2-R supersensitivity in the absence of any known neuropathology.

2 DA Receptor Supersensitization (DA RSS) Following Dopaminergic Denervation in Adulthood

DA RSS is a phenomenon that was encountered from the 1960s onward – a reactive event when dopaminergic nerves were destroyed in adulthood. This process is perhaps best exemplified in some of the original studies in rats by Urban Ungerstedt and colleagues (Ungerstedt, 1971a, b), demonstrating that a proliferation of D_2-R number accompanies the supersensitization event (Creese et al., 1977; Marshall & Ungerstedt, 1977).

3 DA RSS in Neonates

3.1 DA D_1 Receptor Latent and Overt Supersensitization Following Dopaminergic Denervation in Early Postnatal Ontogeny

In the 1960s George Breese and colleagues initiated a series of studies in which the neurotoxin 6-hydroxydopamine (6-OHDA) was administered to newborn rats in order to produce near-total destruction of dopaminergic innervation to the neostriatum. [It is important to relate, that in this and virtually all studies to be described, that 6-OHDA treatments were accompanied by treatment with the norepinephrine transport (NET) inhibitor, desipramine to restrict 6-OHDA toxicity to dopaminergic nerve – with noradrenergic thus being protected and left virtually intact.] The early postnatal 6-OHDA treatment effect was life-long (Breese et al., 1984a, b, 1985a, b). When challenged at a weekly intervals with a DA D_1 receptor (D_1-R) agonist, the behavioral responses of these rats was virtually identical to the responses exhibited by non-lesioned control rats – at least for the first two challenge treatments. However, when the third and subsequent challenge doses of a D_1-R agonist were administered, there was a 5- to 300-fold increase in locomotor and stereotyped responses in rats that had been lesioned neonatally with 6-OHDA (Breese et al., 1985b; Criswell et al., 1989). The ultimate D_1-R agonist-induced production of D_1-R supersensitivity was termed a "priming" process – evolving from "latent" D_1-R sensitivity to overt D_1-R supersensitivity. Moreover, the D_1-R supersensitivity was not accompanied by a change

in the number of D_1-R (i.e., B_{max}) in the striatum (Breese et al., 1985a, b, 1987; Duncan et al., 1987; Criswell et al., 1989; Gong et al., 1994). Also, the 6-OHDA pretreatment with desipramine, in effect, protected – and left intact, noradrenergic neurons – while the SNpc dopaminergic innervation to the striatum was near-totally destroyed.

While repeated adulthood treatments of neonatally 6-OHDA rats with a D_1-R agonist was initially shown to prime D_1-R, it is notable that repeated treatments of these rats with a D_2-R agonist will likewise evoke D_1-R supersensitization (Criswell et al., 1989). Regardless, there is a realization that there can be either homologous (D_1-R agonist) or heterologous (D_2-R agonist) priming of D_1-R. A single treatment with L-3,4-dihydroxyphenylalanine (L-DOPA) will similarly prime D_1-R (Breese et al., 1984a, 1985a, b, 1987).

Neonatal 6-OHDA lesioning of dopaminergic innervation of the neostriatum in rats resulted in reactive serotoninergic sprouting and ensuing serotoninergic hyperinnervation of striatum (Breese et al., 1984a, 1985; Snyder et al., 1986; Stachowiak et al., 1984). Binding of 5-HT was increased in striatum but not globus pallidum of neonatally 6-OHDA-lesioned rats, suggestive of upregulation of 5-HT-R binding sites for striatonigral, not striatopallidal projections (Radja et al., 1993).

Serotoninergic receptors, like)D_1-R also are supersensitized in the neostriatum of neonatally 6-OHDA-lesioned rats. The largely 5-$HT_{1B/2C}$-R agonist m-chlorophenylpiperazine (mCPP) enacts a prominent enhancement of evoked vacuous chewing movements (VCMs, purposeless chewing movements) in such rats – on the first dose (Gong & Kostrzewa, 1992). The presumed 5-HT_{2C}-R supersensitization was greater than D_1-R sensitization, as assessed by the magnitude of the oral activity response.

4 5-HT-R ANTAGONISTS and D_1-RSS

4.1 Overt DA D_1 Receptor Supersensitization Following Dopaminergic Denervation in Early Postnatal Ontogeny

4.1.1 D_1R Supersensitization

In contrast to the priming of D_1R associated with locomotor and most stereotyped responses in rats neonatally lesioned with 6-OHDA, overt D_1R supersensitization is apparent with the first dose of a D_1-R agonist in these rats for oral activity responses (i.e., VCMs). First-dose D_1-R agonist treatment of adult rats that had been lesioned as neonates with 6-OHDA is unaccompanied by a change in B_{max} and K_d in DA-denervated striatum (Huang and Kostrzewa 1994; Kostrzewa & Hamdi, 1991). This effect is repeated for at least 9 months, and is likely a life-long effect (Gong et al., 1992). The overt D_1-R agonist enhancement of oral activity is absent when there is a loss of striatal DA content of 97%, but present if the loss of striatal DA content is greater than 99%; and apparently unrelated to changes in striatal 5-HT up regulation (Gong et al., 1993). In these rats, a DA D_2-R antagonist, alone, similarly evokes increased oral activity responses in the neonatally 6-OHDA-lesioned rats. That effect, curiously, is attenuated by a D_1-R antagonist, implicating a role for D_1-R with the D_2-R antagonist effect (Kostrzewa & Gong, 1991).

4.1.2 5-HT-R Supersensitization

Adult rats that had been lesioned as neonates with 6-OHDA demonstrated enhanced oral activity responses that are likewise observed for serotoninergic agonists. The largely 5-HT_{2C}-R agonist mCPP evokes increased oral activity responses in neonatally 6-OHDA lesioned rats, indicating that 5-HT-R are also supersensitized (Gong & Kostrzewa, 1992). 5-HT_{1A}-R and 5-HT_{1B}-R are seemingly not sensitized; nor do 5-HT_{1A}-R antagonists, 5-HT_{1B}-R antagonists, or 5-HT_3-R antagonists attenuate the enhanced mCPP effect in the lesioned rats. A D_1-R antagonist fails to alter the mCPP enhanced effect on oral activity, but a 5-HT_{2C}-R antagonist does attenuate the D_1-R agonist enhanced effect on oral activity in 6-OHDA-lesioned rats (Gong et al., 1992). Accordingly, the 5-HT_{2C} sensitization may have somewhat of a modulatory role on the D_1-R action, but not vice-versa (Kostrzewa et al., 1992).

When the serotoninergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) was co-administered with neonatal 6-OHDA treatment, D_1-R supersensitization was ablated (Brus et al., 1994), further implicating serotoninergic systems as modulators of D_1-R supersensitization (Brus et al., 1994; Kostrzewa et al., 1992). When 5,7-DHT was administered centrally to adult rats that had been neonatally 6-OHDA-lesioned, D_1-R sensitization was abolished, while 5-HT_{2C}-R sensitization was enhanced – observed as both increases in oral activity and locomotor responses (Kostrzewa et al., 1994).

4.1.3 Cholinergic/Muscarinic-R Supersensitization

In adult rats that had been 6-OHDA-lesioned as neonates, the muscarinic-R agonist pilocarpine evoked enhanced oral activity responses; the enhanced response was attenuated by the muscarinic-R antagonist scopolamine (Kostrzewa & Neely, 1993). Moreover, scopolamine abated enhanced oral activity responses (i.e., VCMs) in these rats to a D_1-R agonist as well as a 5-HT_{2C}-R agonist – implicating dependence of D_1-R actions and 5-HT_{2C}-R actions through cholinergic neural actions (Kostrzewa et al., 1992; Kostrzewa & Neely, 1993).

4.1.4 Intricacies of Neural Phenotypes and Receptor Supersensitization (RSS)

As indicated earlier, in each of the above studies desipramine was a pretreatment with 6-OHDA, thereby maintaining an intact noradrenergic innervation while near-totally destroying dopaminergic innervation from substantia nigra to striatum. Because of the fact that solely dopaminergic neurons and dopaminergic innervation was largely altered, and all other phenotypic systems denoted were essentially intact, save for the groups with add-on 5,7-DHT treatment, DA D_1-R sensitization could be assessed and its dependence on serotoninergic systems with 5-HT_{2c} sensitized receptors could be recognized. Subsequent enactment of these neural phenotypic systems through a cholinergic system with likely M_3-R sensitization could also be ascribed. The phenomenon of receptor supersensitization can be 'dissected', but the interplay and mediation of receptor sensitization must be appreciated in the neural networks of the brain.

4.2 Overt DA D_2 Receptor Supersensitization Following Dopaminergic Denervation in Early Postnatal Ontogeny

In rats 6-OHDA-lesioned in early postnatal ontogeny then given an adulthood challenge dose of the D_2-R agonist quinpirole, there is an enhanced locomotor and stereotypic response to this initial treatment – signaling an overt D_2-R supersentization in these largely dopaminergic denervated rats (Breese et al., 1985a, b). Repeated quinpirole treatments do not prime (i.e., further sensitize) the D_2-R (Breese et al., 1985b; Criswell et al., 1989). D_2-R supersensitization in this instance is not associated with a change in the apparent number (B_{max}), nor D_2-R affinity (K_d) in striatum when spiperone is the ligand (Breese et al., 1987; Luthman et al., 1990), but is associated with an increase in B_{max} when raclopride in the ligand (Dewar et al., 1990; Huang et al., 1997). Adulthood repeated treatment with haloperidol does not increase the B_{max} for D_2-R as is typical for rats with an intact dopaminergic innervation),

5 DA D_2-R Agonist Induction of Long-Lived Dopamine D_2-R Supersensitivity – Neurotoxicity in the Absence of Overt Neuropathology

The definition of a "selective neurotoxin" is now mired, when taking the actions of the DA D_2-R agonist, quinpirole, into account. Repeated quinpirole treatments unexpectedly induce an alteration in the sensing of D_2-R, as eventual exaggerated behavioral responses arise – to the extent that the derived action is abnormal. The supersensitization of D_2-R is long-lived and likely life-long. The abnormal response of the D_2-R is akin to a neurotoxicity, even in the absence of overt neural damage.

In early studies by Henry Szechtman's group, repeated quinpirole treatments were shown to produce enhanced stereotypic and locomotor effects (Eilam et al., 1989). The hyperactivity in quinpirole-treated rats along with their perseveration in routes (restricted paths in an open environment) was considered to be a good model of obsessive-compulsive disorder (Eilam et al., 1989, 2006; Szechtman & Woody, 2004, 2006; Alkhatib et al., 2013). A number of same abnormal stereotypic responses (i.e., licking, grooming, digging, eating) to quinpirole was observed in rats that had been both 6-OHDA lesioned as neonates and treated daily for the first 32 days post-birth with quinpirole (Kostrzewa et al., 1990).

When intact (non-lesioned) rats were treated daily with quinpirole for the first 28 days after birth, subsequent challenge doses of quinpirole produced a dose-related enhanced yawning response in adulthood, despite the fact that there was no change in the B_{max} or K_d for D_2-R (i.e., [^{3}H]spiperone binding in striatum) (Kostrzewa & Brus, 1991). Even ultra-low daily quinpirole treatments (50 μg/day) for as little as 11 consecutive days (P0 [birth] to P11; or P12 to P22; or P23 to P33] produced an enhanced yawning response in adulthood (Kostrzewa et al., 1993a). In contrast to quinpirole priming the D_2-R, the reputedly D_3-R agonist 7-OH-DPAT [(±)-2-(dipropylamine)-7-hydroxy-1,2,3,4-tetrahydronaphthalene] failed to prime a

yawning response to a challenge dose of either quinpirole or 7-OH-DPAT in rats (Oswiecimska et al., 2000).

Rats quinpirole-primed in early postnatal ontogeny exhibited an enhanced quinpirole-antinociceptive effect (hot plate response time) in adulthood (Kostrzewa et al., 1991). Bizarre age-related (P18 through P30) quinpirole-induced vertical jumping with accompanying paw-treading was observed for an hour or more, following quinpirole challenge doses (0.1–3.0 mg/kg). Notably, vertical jumping occurred only if the cage lid was removed. Otherwise jumping was suppressed, so that rats did not harm themselves by hitting against a cage lid (Kostrzewa et al., 1993b). In rats that had been both 6-OHDA lesioned (134 μg, i.c.v., 3 days after birth) as neonates and challenged from birth with daily quinpirole treatments, there was an increase in the number of quinpirole-induced vertical jumps in a session (Kostrzewa & Kostrzewa, 2012). When rats were primed with three increasing doses of quinpirole (25, 50, 100 μg/kg, 1 dose per day), at approximately 2 months of age, subsequent acute amphetamine treatment enhanced striatal DA exocytosis (Nowak et al., 2001). These findings indicate that D_2-R supersensitivity has a presynaptic and postsynaptic component.

In neonatally 6-OHDA-lesioned rats that had addition quinpirole priming during postnatal ontogeny with daily quinpirole treatments (P0–P28), a quinpirole challenge dose (2.6 mg/kg) in adulthood failed to produce an enhanced quinpirole-induced locomotor response. However, quinpirole priming did enhance D_1-R agonist induced locomotor responses in adulthood (Brus et al., 2003). This effect is analogous to adulthood heterologous priming of D_1-R by weekly quinpirole challenge doses in rats that had been lesioned as neonates with 6-OHDA (Criswell et al., 1989).

While DSP-4 [*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamineneonatal] lesioning of noradrenergic innervation prevents ontogenetic quinpirole priming of D_2-R (Nowak et al., 2006), neonatal co-lesioning with DSP-4 and 5,7-DHT results in enhanced quinpirole-induced and 7-OHDA-induced yawning as well as enhanced apomorphine-induced stereotypies (Brus et al., 1995; Nowak et al., 2009). These findings indicate that both noradrenergic and serotoninergic nerves have a prominent influence on the D_2-R priming process.

In quinpirole-primed rats, spatial memory deficits and enhanced skilled reaching were observed in adulthood (Brown et al., 2002) along with enhanced responses to psychostimulants amphetamine (Cope et al., 2010) and nicotine (Brown et al., 2012). Enhanced quinpirole-induced locomotor and stereotyped responses observed in adult rats that were quinpirole primed during postnatal ontogeny are attenuated by acute nicotine pretreatment in adulthood; and this effect was accompanied by increased [^{125}I]α-bungarotoxin binding in striatum and hippocampus and greater [^{3}H]cytisine binding in midbrain and cerebellum. These findings indicate that nicotinic α_7 and $\alpha_4\beta_2$ receptor parameters, respectively, are regionally altered in quinpirole-primed rats (Tizabi et al., 1999). In separate studies, nicotine adulthood treatments (0.3 mg/kg x 2/day) for 14 consecutive days reversed performance deficits in quinpirole-primed rats on the Morris water task and skilled reaching task and partially reversed a 36% decrease of choline acetylcholine transferase in

hippocampus. This finding supports the role of nicotinic receptors in quinpirole priming and projects involvement of cholinergic systems in the priming phenomenon (Brown et al., 2004).

D_2-R supersensitivity is implicated in obsessive-compulsive disorder (Eilam et al., 1989, 2006; Szechtman & Woody, 2004, 2006; Alkhatib et al., 2013) and is regarded as a major component of schizophrenia in which there is an elevation in the number of D_2^{high} receptors (Seeman et al., 2005, 2007; Seeman, 2011). So-called breakthrough DA-R supersensitivity is also regarded as a factor in antipsychotic treatment failure (Samaha et al., 2007).

The process of D_2-R supersensitivity, as relating to quinpirole-induced ontogenetic priming, appears to be a lifelong permanent effect, still evident in rats approaching 2 years of age (Brus et al., 1998; Oswiecimska et al., 2000). Quinpirole induction of D_2-R supersensitivity is discussed in several reviews (Kostrzewa, 1995; Kostrzewa et al., 2004, 2008, 2011, 2018; Nowak et al., 2004; Brown et al., 2012, 2020). Permanent sensitization of D_2-R and resulting alteration of behaviors, despite lack of evidence of neuropathology, is representative of neurotoxicity.

6 Conclusion

The phenomenon of permanent, seemingly life-long, production of dopamine D2 receptor supersensitivity (DARSS) is an abnormality that is expressed as exaggerated and even abnormal behavioral responses to DA (or DA agonist) doses that ordinarily would produce no overt behavioral response. It has been recognized, for decades, that lesioning of dopaminergic innervation in brain is associated with alterations in DA-R status, generally a supersensitization that is overt or induced, "primed," by DA agonist treatments. The induction of DARSS is influenced differently for D1-R versus D2-R, and the Bmax may be increased, but not necessarily so. Production of permanent D2 DARSS, owing to the repeated daily D2-R agonist treatments during early stages of postnatal ontogeny, represents an outcome unaccompanied by changes in dopaminergic innervation, nor in changes in Bmax and Kd (i.e., receptor numbers and receptor affinity, respectively). Both noradrenergic and serotoninergic inputs influence DARSS, while changes in cholinergic/nicotinic receptor status occur. Ontogenetic induction of D2 RSS persists even after lesioning dopaminergic nerves. Significantly, repeated D1-R agonist treatments during postnatal ontogeny do not induce supersensitization of D1R, nor does repeated D1-R agonist treatment alter the sensitization status of DA D2-R. As such, the process of sensitization of D1-R and D2-R, whether occurring after repeated DA agonist treatments after neurodegeneration of a neuronal phenotype, fulfils the definition of an actual neurotoxicity; that status of receptor sensitization is per se a neurotoxicity. Human neurologic disorders and psychiatric disorders are clinical counterparts in which receptor sensitization changes are manifest and thereby become an additional neurotoxicity that enters into a treatment approach.

7 Cross-References

- Cocaine as a Neurotoxin
- Dopamine and L-Dopa as Selective Endogenous Neurotoxins
- Methamphetamine and MDMA Neurotoxicity: Biochemical and Molecular Mechanisms
- Models of Methamphetamine-Induced Neurotoxicity
- Neurotoxicity of Methamphetamine
- *N*-Methyl-(*R*)salsolinol and Enzymes Involved in Enantioselective Biosynthesis, Bioactivation, and Toxicity in Parkinson's Disease
- Survey of Selective Monoaminergic Neurotoxins Targeting Dopaminergic, Noradrenergic, and Serotoninergic Neurons

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