Neurotoxicity Research, 2008, VOL. 14(2,3). pp. 121-128

F.P. Graham Publishing Co.

Dopamine Receptor Supersensitivity: Development, Mechanisms, Presentation, and Clinical Applicability

RICHARD M. KOSTRZEWA[a,*], JOHN P. KOSTRZEWA[a], RUSSELL W. BROWN[b], PRZEMYSLAW NOWAK[c] and RYSZARD BRUS[c]

[a]*Department of Pharmacology, Quillen College of Medicine; and* [b]*Department of Psychology, East Tennessee State University, Johnson City, TN 37614, USA; and* [c]*Department of Pharmacology, Medical University of Silesia, 41-808 Zabrze, Poland. kostrzew@etsu.edu*

(Submitted 21 October 2007; Revised 21 January 2008; In final form 22 February 2008)

The process of receptor supersensitivity (RSS) has a long history and is an epiphenomenon of neuronal denervation. Dopamine (DA) RSS (DARSS) similarly occurs after DA-denervation, and this process is invoked in neuropsychiatric and neurodegenerative disorders. From studies largely over the past 25 years, much has been learned regarding DARSS. For example, overt D_1 DARSS occurs after perinatal destruction of nigrostriatal DA fibers. However, following perinatal destruction of DA innervation, the most-prominent behavioral effects of a D_1 agonist are observed after a series of D_1 agonist treatments - a process known as *priming* of D_1 DA receptors. Moreover, perinatal lesioning of DA fibers produces prominent serotonin (5-HT) RSS, and in fact 5-HT RSS appears to modulate D_1 DA RSS. In rodents, receptor supersensitization by these means appears to be irreversible. In contrast to the observed D_1 DARSS, D_2 DARSS apparently does not occur after perinatal DA denervation. Also, while repeated D_1 agonist treatment of intact rats has no observable effect, repeated D_2 agonist treatments, during or after the ontogenetic phase, produces prominent life-long D_2 RSS. The process may have an association with substance abuse. Therefore, production of D_1 and D_2 DARSS occurs by different means and under different circumstances, and in association with perhaps different neuronal phenotypes, and with greater incidence in either intact (D_2) or DA-lesioned counterparts (D_1). The physiological consequence of RSS are multiple.

Keywords: Receptor supersensitivity; Dopamine; Serotonin; Priming; Denervation

INTRODUCTION

The study of psychoactive drugs in non-human species is complicated by the fact that we are unable to know what animals think or whether they are emotionally affected by a drug treatment. Because the majority of initial drug assessments are performed in rodents, the problem is more compounded, because rodents generally fail to even display motor syndromes that might be produced in humans. A reductionist approach, then, has evolved, whereby rodents are observed for drug-induced stereotypies - and this has proved to be a reasonable means of assessing (at least) dopamine (DA) receptor involvement. With the mixed DA D_1/D_2 agonist apomorphine one can initially observe salivation; and with

*Corresponding author: Tel.: 1 (423) 439-6321; FAX: 1 (423) 439-8773; kostrzew@etsu.edu

ISSN 1029 8428 print/ ISSN 1476-3524 online.

a higher dose, salivation accompanied by occasional gnawing - which evolves to salivation and repeated gnawing; the latter effect, with running around the cage, occurs at a high dose of apomorphine (Costall *et al.*, 1975). Breese *et al.* (1985a,b; 1987) described a host of other stereotypic behaviors aroused by D_1 and D_2 agonist treatments, including digging, grooming, rearing, paw-treading, taffy-pulling, self-biting, self-mutilation, and other stereotypies.

Another widely accepted means of gauging receptor activation or extent of sensitivity is with the so-called 'Ungerstedt' rodent. For example, when either the nigrostriatal tract or medial forebrain bundle (through which the nigrostriatal tract projects) is lesioned, the consequent DA-denervation of striatum (basal ganglia) results in the development of DA receptor supersensitivity (RSS; DARSS). This process, taking several days and maximizing by ~2 weeks after a lesion, results in exaggerated behaviors by (graded) low doses of a DA agonist that would produce virtually no effect in sham operated controls. When the lesion is made only on one side, agonists acting on supersensitized receptors on the lesioned side result in circling behavior - because one side is more stimulated than the other (Ungerstedt, 1971b,c).

The development of RSS is the normal 'adaptive' response to denervation, and it has been recognized for more than a century, as evidenced by greatly enhanced responsiveness of denervated muscle to nicotine. Because the majority of psychoactive drugs affect DA receptors in both the nigrostriatal motor pathway and the mesolimbic mood-related pathway, DARSS represents a reasonable means of gauging central actions of such drugs.

In studies in our laboratory, we have been engaged primarily in denervation studies, generally utilizing neurotoxins for monoaminergic nerves (*i.e.*, DA, norepinephrine [NE], serotonin [*i.e.*, 5-hydroxytryptamine, 5-HT]). This review article is intended to systematically characterize some of the features inherent in RSS and relate them to clinical phenomena.

6-HYDROXYDOPAMINE LESIONING OF DA NERVES

The neurotoxin 6-hydroxydopamine (6-OHDA) is highly selective for catecholamine nerves, by virtue of its high affinity for the DA transporter (DAT) and NE transporter (NET), ultimately being accumulated by these nerves to a high level in the cytoplasm whereby high levels of reactive oxygen species are generated (see Kostrzewa and Jacobowitz, 1974). Subsequent impairment of mitochondrial oxidative phosphorylation results in energy depletion and initiation of neuronal apoptosis, coupled with necrosis. Destruction of DA or NE nerve endings, and possibly cell bodies (according to dose), results in DA-denervation and/or NE-denervation of brain sites and the development of DARSS and/or NE RSS.

When 6-OHDA is administered into the cerebral ventricles or cisterna of newborn rodents, a similar outcome prevails. For the NE system, destruction of NE fibers in the dorsal bundle is associated with marked NE fiber denervation of regions distal from the nucleus of origin (namely the locus coeruleus), so that the neocortex, hippocampus, and spinal cord are largely NE-denervated for the remainder of life. In contrast, there is reactive sprouting of short NE axons, resulting in NE hyperinnervation of regions close to the locus coeruleus, such as the midbrain, pons, medulla, and cerebellum. This NE hyperinnervation is also life-long (Jonsson *et al.*, 1974; Kostrzewa and Harper, 1974; Kostrzewa and Garey, 1976; 1977).

For the DA system, high dose 6-OHDA produces near-total destruction of the nigrostriatal tract in neonates, typically resulting in >95% loss of DA innervation to the striatum (Breese *et al.*, 1984; 1985a,b; 1987; Berger *et al.*, 1985; Snyder *et al.*, 1986). However, because ventral tegmental neurons have far fewer DATs, this system is not prominently compromised by neonatal 6-OHDA treatment (Okamura *et al.*, 1995). By gross observation such lesioned rats, with the striatum DA-denervated, are virtually indistinguishable from intact rats. In other words, they are mobile and they eat and drink to a similar extent as intact rats (Breese *et al.*, 1985a,b). Only by exacting behaviorial assessments is one able to recognize striatal DA-denervation, behaviorally. In contrast, when 6-OHDA is administered to adult rats, there may be still 20% or more of DA innervation remaining in the striatum; yet, these rats become aphagic, adipsic, and akinetic - resembling Parkinsonian rats (Ungerstedt, 1971a; see Zigmond and Stricker, 1989). With nurturing

and special care for the next two weeks these rats can recover to some extent and still live, but precariously. By comparison, the unilaterally DA-lesioned rat (*i.e.*, Ungerstedt rat; Ungerstedt, 1971c) is able to eat, drink and remain mobile and thus survive without special care.

5,7-DIHYDROXYTRYPTAMINE LESIONING OF 5-HT NERVES

The neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) owes its relatively selective action on 5-HT nerves to the fact that 5,7-DHT has high affinity for the 5-HT transporter (SERT, 'serotonin transporter') (Baumgarten *et al.*, 1973). When selectively accumulated by 5-HT nerves, 5,7-DHT promotes reactive oxygen species formation in the cytoplasm, resulting in impaired oxidative phosphorylation, energy depletion, and induction of both apoptotic and necrotic processes. Its cellular mechanism of action is much like that of 6-OHDA. When administered to adult rats, 5,7-DHT produces prominent 5-HT-denervation of brain; when administered to neonatal rats, 5,7-DHT produces ~90% destruction of 5-HT innervation of forebrain, neocortex, and hippocampus. Behaviorally, except by special testing, these rats are indistinguishable from controls (see Baumgarten and Lachenmayer, 2004).

NEONATAL 6-OHDA AND DA D_1 RSS

Latent D_1 DARSS and the Priming Phenomenon

As indicated, when 6-OHDA (100-200 μg) is administered in high dose (Kostrzewa *et al.*, 1993a) to rats within one week of birth (Gong *et al.*, 1993b), >95% reduction in striatal DA-innervation occurs, resulting in latent DARSS. These rats display spontaneous hyperlocomotor activity from 2-3 weeks after birth (Shaywitz *et al.*, 1976a,b), and sometimes into adulthood, particularly if serotoninergic nerves in brain are lesioned in adulthood with 5,7-DHT (Kostrzewa *et al.*, 1994). Lesioned rats, even as adults, are nearly indistinguishable from control even after the first or second dose of the DA D_1 agonist SKF 38393 (Breese *et al.*, 1985a,b). However, the 3rd and all subsequent doses of SKF 38393 produce intense behavioral stereotypies (of many forms) accompanied by an abnormally high level of locomotor activity (Breese *et al.*, 1985a,b; Gong *et al.*, 1993a; 1994). This 'unmasking' of D_1 DARSS by repeated doses of a D_1 agonist at spaced intervals is known as *priming* - a term coined by Breese. In addition to this homologous *priming* (*i.e.*, D_1 agonist induction of D_1 RSS), it is possible to supersensitize the D_1 receptor by repeated D_2 agonist treatments, a process termed heterologous *priming* (Criswell *et al.*, 1989). For example, when the D_2 agonist quinpirole is administered twice, with a one-week interval, a later treatment with first-time SKF 38393 produces an abnormally high number of stereotypies and hyperlocomotor activity, ananogous to that observed after 3 separate doses of SKF 38393. DARSS in such rats is life-long (Criswell *et al.*, 1989). The effects of this and other treatments are summarized in Table I.

When neonatally 6-OHDA-lesioned rats are repeatedly treated in adulthood with the D_2 agonist quinpirole, the third and subsequent doses of quinpirole do not produce the markedly exaggerated stereotyped and locomotor effects - unlike that observed with repeated D_1 agonist treatments in such rats (Brus *et al.*, 2003). Thus, *priming*, as per the D_1 receptor, is not observed for the D_2 receptor in neonatally 6-OHDA-lesioned rats.

Table I Potential of a dopamine D_1 agonist, D_2 agonist and 5-HT_2 agonist to produce DARSS on the first dose or after repeated dosing (*i.e., priming*) in intact rats, neonatally 6-OHDA-lesioned rats (n6-OHDA) or in adulthood 6-OHDA-lesioned rats (a6-OHDA).

Animal Group	D_1 Agonist Dosing		D_2 Agonist Dosing		5-HT_2 Agonist Dosing	
	Single	Repeated	Single	Repeated	Single	Repeated
Intact Rats	—	—	—	+++	—	—
n6-OHDA Rats	—	++++	±	—	+++	+++
a6-OHDA Rats	++	++	++	++	?	?

—, no effect; ±, minor effect or no effect; ?, unknown effect or not well-studied
++, moderate effect; +++, large effect; ++++, mafor effect

Overt D_1 DARSS in Neonatally 6-OHDA-lesioned Rats

According to the particular behavior under study, it is possible to observe overt D_2 DARSS in neonatally 6-OHDA-lesioned rats (*i.e.*, after the first SKF 38393 dose). Rosengarten *et al.* (1982) observed that a high dose of the D_1 agonist SKF 38393 produced vacuous chewing movements (VCMs) in intact rats. However, when the first dose of SKF 38393 was administered in adulthood to rats that were lesioned neonatally with 6-OHDA, VCMs were observed with a dose of SKF 38393 that was 100- to 1000-fold lower than the effective dose in intact rats (Kostrzewa and Gong, 1991; Gong *et al.*, 1993a). Accordingly, this effect demonstrates that there is overt D_1 DARSS in neonatally 6-OHDA-lesioned rats (*i.e.*, enhanced behavior, vs intact rats, after the first D_1 agonist dose) (see Table I).

NEONATAL 6-OHDA AND 5-HT RSS

It is not so unusual, that D_1 DARSS would develop subsequent to DA-denervation, although the contrast between overt DARSS versus the *priming* phenomenon relating to DARSS is interesting. However, quite surprising, is the fact that there is an enhanced behavioral response (VCMs) to the first dose of a 5-HT agonist in adult rats that had been lesioned neonatally with 6-OHDA (Gong and Kostrzewa, 1992; Gong *et al.*, 1992; 1993b). In fact, the predominately 5-HT_2 agonist, m-chlorophenylpiperazine (mCPP), produced a higher maximum number of VCMs than a D_1 agonist (Gong and Kostrzewa, 1992). Thus, 5-HT_2 receptors are overtly supersensitized after neonatal DA-denervation of striatum. This is notable, since a later study demonstrated that the mCPP induction of VCMs occurs after direct injection of mCPP into the striatum (Plech *et al.*, 1995) (see Table I).

It is of particular note that 5-HT fiber hyperinnervation of striatum and forebrain ensues consequent to a neonatal 6-OHDA lesioning of DA innervation (Kostrzewa *et al.*, 1998). 5-HT fiber hyperinnervation is fully developed by 4-6 weeks and it persists life-long in the neonatally 6-OHDA-lesioned rats (Berger *et al.*, 1985; Snyder *et al.*, 1986; Luthman *et al.*, 1987; Towle *et al.*, 1989; Descarries *et al.*, 1992; Molina-Holgado *et al.*, 1994; Soucy *et al.*, 1994; Mrini *et al.*, 1995). Although one might expect RSS to arise following denervation, in the described scenario, 5-HT RSS arises when there is presynaptic 5-HT receptor proliferation (Radja *et al.*, 1993b) and 5-HT fiber hyperinnervation (El Mansari *et al.*, 1994).

Other neuronal phenotypic systems are also influenced by perinatal dopaminolytic effects. Cholinergic muscarinic receptors are sensitized (Kostrzewa and Neely, 1993), as are histaminic H_3 receptors (Nowak *et al.*, 2006). Moreover, the noradrenergic system additionally impacts on DA RSS, as D_2 RSS occurs when both the noradrenergic and serotoninergic systems are damaged perinatally (Nowak *et al.*, unpublished).

In related studies on this theme, Huang *et al.* (1997) followed the protocol of Waddington to study tardive dyskinesia mechanisms, by administering haloperidol in drinking water of rats, for one year. While the time-course of tardive dyskinesia in intact rats, evidenced as an increase in spontaneous VCMs, mirrored that in the Waddington study, there was an accelerated time-course of the increase in VCM number in haloperidol-treated 6-OHDA-lesioned rats. Moreover, there was a doubling of the number of spontaneous VCMs in the haloperidol-treated lesioned rats vs haloperidol-treated DA-intact rats (Huang *et al.*, 1997). The effect persisted for the 1-year duration of haloperidol treatment, and it was accompanied by an increase in the B_{max} for striatal D_2 receptors. Notably, after haloperidol was withdrawn as a treatment, the high number of VCMs persisted in these rats for 8 months (Huang and Kostrzewa, 1994), at which time the study terminated. At the end of this 8-month haloperidol-free period, the B_{max} for D_2 receptors was at the level found in intact untreated rats, indicating that VCM number was thus unrelated to D_2 receptor number (Huang *et al.*, 1997). This finding supports earlier observations that the phenomenon of DA RSS appears to be unrelated to numbers of D_1 or D_2 receptors (Breese *et al.*, 1985a,b; Kostrzewa and Brus, 1991; Gong *et al.*, 1994; Kostrzewa, 1995), although there is not full agreement on this point (Radja *et al.*, 1993a; Dewar *et al.*, 1990).

5-HT AND D_1 DARSS IN NEONATALLY 6-OHDA-LESIONED RATS

Interaction between 5-HT and DA systems, over time, has been the subject of only occasional study. However, in neonatally 6-OHDA-lesioned rats,

studied as adults, there is a prominent influence of the 5-HT system on the DA system. For example, in rats co-lesioned as neonates with both 6-OHDA and 5,7-DHT in order to largely destroy DA and 5-HT innervation of brain, overt D_1 RSS does not develop (Brus *et al.*, 1994). Moreover, when neonatally 6-OHDA-lesioned rats are lesioned as adults with 5,7-DHT, the overt D_1 RSS, as reflected by enhanced SKF 38393-induced VCMs, is attenuated (unpublished). Therefore, it appears that 5-HT fibers have a regulatory/modulatory effect on the maintenance of D_1 DA RSS. Moreover, in the neonatally 6-OHDA-lesioned rats that are lesioned in adulthood with 5,7-DHT, there is development of D_2 DARSS (Brus *et al.*, 1995). This indicates further, that 5-HT innervation has a 'suppressor' effect on the sensitivity level of D_2 receptors in rats that were largely DA-denervated as neonates. This phenomenon is noteworthy particularly in regards to treatment of Lesch-Nyhan children (Breese *et al.*, 1990; 2005).

When neonatally 6-OHDA-lesioned rats are pretreated with the 5-HT receptor antagonist mianserin, there is demonstrable suppression of D_1 agonist-induction of VCMs (Gong *et al.*, 1992). The effect appears to be related to 5-HT_2 receptors, since 5-HT_1 and 5-HT_3 antagonists do not suppress D_1 agonist-induced effects. Moreover, since ketanserin does not abate the D_1 agonist effect, it appears that the 5-HT_{2C} receptor subtype is most prominently involved in 5-HT modulation of D_1 DARSS (Gong *et al.*, 1992).

It is particularly noteworthy that 5-HT hyperinnervation arises when DA denervation occurs neonatally; and that 5-HT RSS occurs simultaneously. Also, the 5-HT system, seemingly via 5-HT_{2C} receptors, governs the sensitivity level of DA receptors. This phenomenon may relate to a preservation of behavior by an alternate neuronal phenotypic system in brain. Clinically, this may translate to the possibility of there being a redundant system that can be aroused under proper circumstances, perhaps as a new modality in treating psychiatric and neurodegenerative disorders in humans.

OCCURRENCE OF DA D_2 RSS IN THE ABSENCE OF A LESION

In an attempt to better understand mechanisms attending RSS, we took the approach of simply treating intact rats once a day with a DA agonist, starting from birth. In rats treated with the D_1 agonist SKF 38393, once a day for the first 28 days after birth, there was no apparent alteration in D_1 RSS in adulthood. In other words, repeated D_1 agonists did not *prime* D_1 receptors if DA innervation developed without interruption (Gong *et al.*, 1993b; 1994).

When the D_2 agonist quinpirole was administered to intact rats, once a day for the first 28 days after birth, we observed a darting-like behavior in rats starting at 19 days after birth (Kostrzewa *et al.*, 1993c). If rats were in the home cage with a lid, the only other behavior of note was intense eating immediately after quinpirole treatment (Kostrzewa *et al.*, 1990). However, if these same rats were placed in a cage that did not have a lid in place, the quinpirole-treated rats stood upright on hindlimbs for much of the next hour (or hours, when a high dose of quinpirole was administered) and they began jumping like basketball players (*i.e.*, standing upright and jumping) in conjunction with prominent paw-treading. This behavior was dependent on the acute dose for quinpirole, and the jumping behavior persisted for only ~21 to ~28 days after birth (Kostrzewa *et al.*, 1993c). In order words, the behavioral effect was age-specific.

When such rats were studied later in adulthood, D_2 *primed* rats displayed enhanced D_2 agonist induced antinociception (Kostrzewa *et al.*, 1991). Also, acute quinpirole treatment induced yawning - which occurred to a higher maximum than in controls and with a lower quinpirole dose than in controls (Kostrzewa and Brus, 1991). This effect, or D_2 RSS, was life-long (see Table I). Moreover, it was produced even if rats were treated for 11 consecutive days, either from 1) the day of birth to the 11th day after birth, 2) the 12th to 22nd day after birth, or 3) the 23rd to 33rd days after birth (Kostrzewa *et al.*, 1993b). Notably, the predominate D_3 agonist 7-hydroxy-*N,N*-dipropyl-2-aminotetralin (7-OH-DPAT) did not *prime* for the yawning response (Oswiecimska *et al.*, 2000).

It is of interest that repeated D_2 agonist treatments produce life-long D_2 RSS when DA innervation is intact in brain, but repeated D_2 agonist treatments purportedly do not induce D_2 DARSS when DA innervation is largely destroyed in brain from birth. Because many abused drugs act on or via DA sys-

tems (*e.g.*, amphetamines, cocaine), the induction of D_2 RSS by repeated D_2 agonist treatments (in fully DA-innervated brain) may have relevance to substance abuse (Palomo *et al.*, 2002).

MECHANISMS INVOLVED IN DARSS

Despite the search for underlying mechanisms of DARSS, there has been no obvious second messenger system that can account for the phenomenon. Numbers and affinity of high-affinity D_1 receptors remain unaltered when D_1 RSS is present (Gong *et al.*, 1994). Also, c-fos and other second messenger systems remain unchanged or little altered vs control, by acute agonist treatments that are associated with exaggerated D_1 agonist-induced behavior (Johnson *et al.*, 1992; Gong *et al.*, 1994). Thusfar, the major association is a 5-fold enhancement of amphetamine-induced release of striatal DA in rats that had been repeatedly quinpirole-treated during postnatal development. Consequently, one must consider the possibility that DA receptor "supersensitivity" could very well represent DA autoreceptor "subsensitivity" (Nowak *et al.*, 2001). In other words if the indirect acting DA agonist, amphetamine, releases a greater amount of DA in quinpirole-sensitized rats, subsensitivity of autoreceptors on DA nerves could account for the effect, *i.e.*, less DA suppression of further DA release following acute amphetamine treatment. Additional study is needed to resolve the problem.

SUMMARY OF DARSS

DARSS arises under a variety of circumstances. It seems intuitive that D_1 DARSS occurs following DA-denervation. Yet, for D_1 agonist-induced locomotor effects and for most of the stereotypies observed, this D_1 RSS occurs only after *priming* (*i.e.*, repeated D_1 RSS). Even repeated D_2 agonist treatments promote *priming* of D_1 RSS. In contrast to D_1 RSS, DA-denervation does not evoke obvious or prominent D_2 RSS. Thus, not all types of DA receptors are supersensitized by DA denervation.

The expression of D_1 RSS, moreover, is dependent on the modulatory actions of 5-HT nerves. When 5-HT nerves are destroyed, D_1 RSS is either eliminated or suppressed. In the systems studied thusfar, the 5-HT_{2C} receptor subtype appears to have the greatest impact on 5-HT modulation of DA RSS.

While the sensitivity level of D_2 receptors is apparently not prominently altered by DA denervation, the D_2 receptor is readily and greatly sensitized by regular treatments with a D_2 agonist; and the effect is seemingly life-long. Studies by Szechtman and Woody (2006) implicate this particular phenomenon is the obsessive compulsive behavior occurring in humans. This phenomenon also has overlay with substance abuse.

The process of DARSS has been implicated in psychiatric and neurodegenerative disorders. To better approach like-long treatments of CNS disorders, it is important to have a good understanding of DARSS and factors or elements that may give rise to its occurrence, as well as a means of suppressing DARSS. This paper is intended to present an overview of DARSS, and highlight directions for future research.

References

Baumgarten HG and L Lachenmayer (2004) Serotonin neurotoxins - past and present. *Neurotox. Res.* **6**(7-8), 589-614. Review.

Baumgarten HG, A Bjorklund, L Lachenmayer and A Nobin (1973) Evaluation of the effects of 5,7-dihydroxytryptamine on serotonin and catecholamine neurons in the rat CNS. *Acta Physiol. Scand.* Suppl. **391**, 1-19.

Berger TW, S Kaul, EM Stricker and MJ Zigmond (1985) Hyperinnervation of the striatum by dorsal raphe afferents after dopamine-depleting brain lesions in neonatal rats. *Brain Res.* **336**, 354-358.

Breese GR, AA Baumeister, TJ McCown, SG Emerick, GD Frye, K Crotty and RA Mueller (1984) Behavioural differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. *J. Pharmacol. Exp. Ther.* **231**, 343-354.

Breese GR, AA Baumeister, TC Napier, GD Frye and RA Mueller (1985a) Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. *J. Pharmacol. Exp. Ther.* **235**, 287-295.

Breese GR, TC Napier and RA Mueller (1985b) Dopamine agonist-induced locomotor activity in rats treated with 6-hydroxydopamine at differing ages: Functional supersensitivity of D-1 dopamine receptors in neonatally-lesioned rats. *J. Pharmacol. Exp. Ther.* **234**, 447-455.

Breese GR, GE Duncan, TC Napier, SC Bondy, LC Iorio and RA Mueller (1987) 6-Hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D_1- and D_2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. *J. Pharmacol. Exp. Ther.* **240**, 167-176.

Breese GR, HE Criswell, GE Duncan and RA Mueller (1990)

A dopamine deficiency model of Lesch-Nyhan disease - the neonatal-6-OHDA-lesioned rat. *Brain Res. Bull.* **25**(3), 477-484. Review.

Breese GR, DJ Knapp, HE Criswell, SS Moy, ST Papadeas and BL Blake (2005) The neonate-6-hydroxydopamine-lesioned rat: a model for clinical neuroscience and neurobiological principles. *Brain Res. Brain Res. Rev.* **48**, 57-73. Review.

Brus R, RM Kostrzewa, KW Perry and RW Fuller (1994) Supersensitization of the oral response to SKF 38393 in neonatal 6-hydroxydopamine-lesioned rats is eliminated by neonatal 5,7-dihydroxytryptamine treatment. *J. Pharmacol. Exp. Ther.* **268**, 231-237.

Brus R, A Plech and RM Kostrzewa (1995) Enhanced quinpirole responses in rats lesioned neonatally with 5,7-dihydroxytryptamine. *Pharmacol. Biochem. Behav.* **50**, 649-653.

Brus R, RM Kostrzewa, P Nowak, K Perry and JP Kostrzewa (2003) Ontogenetic quinpirole treatments fail to prime for D_2 agonist-enhancement of locomotor activity in 6-hydroxydopamine-lesioned rats. *Neurotox Res.* **5**, 329-338.

Costall B, RJ Naylor and JL Neumeyer (1975) Differences in the nature of the stereotyped behaviour induced by aporphine derivatives in the rat and in their actions in extrapyramidal and mesolimbic brain areas. *Eur. J. Pharmacol.* **31**, 1-16.

Criswell H, RA Mueller and GR Breese (1989) Priming of D_1-dopamine receptor responses: long-lasting behavioral supersensitivity to a D_1-dopamine agonist following repeated administration to neonatal 6-OHDA-lesioned rats. *J. Neurosci.* **9**, 125-133.

Descarries L, J-J Soghomonian, S Garcia, G Doucet and JP Bruno (1992) Ultrastructural analysis of the serotonin hyperinnervation in adult rat neostriatum following neonatal dopamine denervation with 6-hydroxydopamine. *Brain Res.* **569**, 1-13.

Dewar KM, JJ Soghomonian, JP Bruno, L Descarries and TA Reader (1990) Elevation of dopamine D_2 but not D_1 receptors in adult rat neostriatum after neonatal 6-hydroxydopamine denervation. *Brain Res.* **536**, 287-296.

El Mansari M, F Radja, A Ferron, TA Reader, E Molina-Holgado and L Descarries (1994) Hypersensitivity to serotonin and its agonists in serotonin-hyperinnervated neostriatum after neonatal dopamine denervation. *Eur. J. Pharmacol.* **261**, 171-178.

Gong L and RM Kostrzewa (1992) Supersensitized oral response to a serotonin agonist in neonatal 6-OHDA treated rats. *Pharmacol. Biochem. Behav.* **41**, 621-623.

Gong L, RM Kostrzewa, RW Fuller and KW Perry (1992) Supersensitization of the oral response to SKF 38393 in neonatal 6-OHDA-lesioned rats is mediated through a serotonin system. *J. Pharmacol. Exp. Ther.* **261**, 1000-1007.

Gong L, RM Kostrzewa, R Brus, RW Fuller and KW Perry (1993a) Ontogenetic SKF 38393 treatments sensitize dopamine D_1 receptors in neonatal 6-OHDA-lesioned rats. *Dev. Brain Res.* **76**, 59-65.

Gong L, RM Kostrzewa, KW Perry and RW Fuller (1993b) Dose-related effects of a neonatal 6-OHDA lesion on SKF 38393- and *m*-chlorophenylpiperazine-induced oral activity responses of rats. *Dev. Brain Res.* **76**, 233-238.

Gong L, RM Kostrzewa and C Li (1994) Neonatal 6-OHDA and adult SKF 38393 treatments alter dopamine D_1 receptor mRNA levels: absence of other neurochemical associations with the enhanced behavioral responses of lesioned rats. *J. Neurochem.* **63**, 1282-1290.

Huang NY and RM Kostrzewa (1994) Persistent oral dyskinesias in haloperidol-withdrawn neonatal 6-hydroxydopamine-lesioned rats. *Eur. J. Pharmacol.* **271**, 433-437.

Huang N-Y, RM Kostrzewa, C Li, KW Perry and RW Fuller (1997) Persistent spontaneous oral dyskinesias in haloperidol-withdrawn rats neonatally lesioned with 6-hydroxydopamine: absence of an association with the B_{max} for [^{3}H] raclopride binding to neostriatal homogenates. *J. Pharmacol. Exp. Ther.* **280**, 268-276.

Johnson KB, HE Criswell, KF Jensen, PE Simson, RA Mueller and GR Breese (1992) Comparison of the D_1 dopamine agonists SKF 38393 and A 6890 in neonatal 6-hydroxydopamine-lesioned rats: behavioral effects and induction of c-fos-like immunoreactivity. *J. Pharmacol. Exp. Ther.* **262**, 855-865.

Jonsson G, C Pycock, K Fuxe and C Sachs (1974) Changes in the development of central noradrenaline neurons following neonatal administration of 6-hydroxydopamine. *J. Neurochem.* **22**, 419-426.

Kostrzewa RM (1995) Dopamine receptor supersensitivity. *Neurosci. Biobehav. Rev.* **19**, 1-17.

Kostrzewa RM and R Brus (1991) Ontogenic homologous supersensitization of quinpirole-induced yawning in rats. *Pharmacol. Biochem. Behav.* **39**, 517-519.

Kostrzewa RM and RE Garey (1976) Effects of 6 hydroxydopa on noradrenergic neurons in developing rat brain. *J. Pharmacol. Exp. Ther.* **197**, 105 118.

Kostrzewa RM and RE Garey (1977) Sprouting of noradrenergic terminals in rat cerebellum following neonatal treatment with 6 hydroxydopa. *Brain Res.* **124**, 385 391.

Kostrzewa RM and L Gong (1991) Supersensitized D_1 receptors mediate enhanced oral activity after neonatal 6-OHDA. *Pharmacol. Biochem. Behav.* **39**, 677-682.

Kostrzewa RM and JW Harper (1974) Effects of 6 hydroxydopa on catecholamine-containing neurons in brains of newborn rats. *Brain Res.* **69**, 174 181.

Kostrzewa RM and D Jacobowitz (1974) Pharmacological actions of 6-hydroxydopamine. *Pharmacol. Rev.* 26, 199-288.

Kostrzewa RM and D Neely (1993) Enhanced pilocarpine-induced oral activity responses in neonatal 6-OHDA-treated rats. *Pharmacol. Biochem. Behav.* **45**, 737-740.

Kostrzewa RM, A Hamdi and FP Kostrzewa (1990) Production of prolonged supersensitization of dopamine D_2 receptors. *Eur. J. Pharmacol.* **183**, 1411-1412.

Kostrzewa RM, R Brus and J Kalbfleisch (1991) Ontogenetic homologous sensitization to the antinociceptive action of quinpirole in rats. *Eur. J. Pharmacol.* **209**, 157-161.

Kostrzewa RM, R Brus, KW Perry and RW Fuller (1993a) Age-dependence of a 6-hydroxydopamine lesion on SKF 38393- and *m*-chlorophenylpiperazine-induced oral activity responses of rats. *Dev. Brain Res.* **76**, 87-93.

Kostrzewa RM, R Brus, M Rykaczewska and A Plech (1993b) Low dose quinpirole ontogenically sensitizes to quinpirole-

induced yawning in rats. *Pharmacol. Biochem. Behav.* **44**, 487-489.

Kostrzewa RM, J Guo and FP Kostrzewa (1993c) Ontogenetic quinpirole treatments induce vertical jumping activity in rats. *Eur. J. Pharmacol.* **239**, 183-187.

Kostrzewa RM, R Brus, JH Kalbflesich, KW Perry and RW Fuller (1994) Proposed animal model of attention deficit hyperactivity disorder. *Brain Res. Bull.* **34**, 161-167.

Kostrzewa RM, TA Reader and L Descarries (1998) Serotonin neural adaptations to ontogenetic loss of dopamine neurons in rat brain. *J. Neurochem.* **70**, 889-898.

Luthman J, B Bolioli, T Tustsumi, A Verhofstad and G Jonsson (1987) Sprouting of striatal nerve terminals following selective lesion of nigro-striatal dopamine neurons in neonatal rat. *Brain Res. Bull.* **19**, 269-274.

Molina-Holgado E, KM Dewar, L Descarries and TA Reader (1994) Altered dopamine and serotonin metabolism in the dopamine-denervated and serotonin-hyperinnervated neostriatum of adult rat after neonatal 6-hydroxydopamine. *J. Pharmacol. Exp. Ther.* **270**, 713-721.

Mrini A, J-P Soucy, F Lafaille, P Lemoine and L Descarries (1995) Quantification of the serotonin hyperinnervation in adult rat neostriatum after neonatal 6-hydroxydopamine lesion of nigral dopamine neurons. *Brain Res.* **779**, 303-308.

Nowak P, R Brus and RM Kostrzewa (2001) Amphetamine-induced enhancement of neostriatal in vivo microdialysate dopamine content in rats, quinpirole-primed as neonates. *Pol. J. Pharmacol.* **53**, 319-329.

Nowak P, L Labus, RM Kostrzewa and R Brus (2006) DSP-4 prevents dopamine receptor priming by quinpirole. *Pharmacol. Biochem. Behav.* **84**, 3-7.

Okamura H, C Yokoyama and Y Ibata (1995) Lateromedial gradient of the susceptibility of midbrain dopaminergic neurons to neonatal 6-hydroxydopamine toxicity. *Exp. Neurol.* **136**, 136-142.

OÑwi"cimska J, R Brus, R Szkilnik, P Nowak and RM Kostrzewa (2000) 7-OH-DPAT, unlike quinpirole, does not prime a yawning response in rats. *Pharmacol. Biochem. Behav.* **67**, 11-15.

Palomo T, T Archer, RJ Beninger and RM Kostrzewa (2002) Neurodevelopmental liabilities of substance abuse. *Neurotox. Res.* **4**, 267-279.

Plech A, R Brus, JH Kalbfleisch and RM Kostrzewa (1995) Enhanced oral activity responses to intrastriatal SKF 38393 and m-CPP are attenuated by intrastriatal mianserin in neonatal 6-OHDA-lesioned rats. *Psychopharmacology (Berl.)* **119**, 466-473.

Radja F, M El Mansari, J-J Soghomonian, KM Dewar, A Ferron, TA Reader and L Descarries (1993a) Changes in D_1 and D_2 receptors in adult rat neostriatum after neonatal dopamine denervation: quantitative data from ligand binding, *in situ* hybridization and iontophoresis. *Neuroscience* **57**, 635-648.

Radja F, L Descarries, KM Dewar and TA Reader (1993b) Serotonin 5-HT_1 and 5-HT_2 receptors in adult rat brain after neonatal destruction of nigrostriatal dopamine neurons: a quantitative autoradiographic study. *Brain Res.* **606**, 273-285.

Rosengarten H, JW Schweitzer and AJ Friedhoff (1982) Induction of oral dyskinesias in naive rats by D_1 stimulation. *Life Sci.* **19**, 33, 2479-2482.

Shaywitz BA, JH Klopper and JW Gordon (1976a) Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine. *Nature* **261**, 153-155.

Shaywitz BA, RD Yager and JH Klopper (1976b) Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. *Science* **191**, 305-308.

Snyder AM, MJ Zigmond and RD Lund (1986) Sprouting of serotonergic afferents into striatum after dopamine depleting lesions in infant rats: a retrograde transport and immunocytochemical study. *J. Comp. Neurol.* **245**, 274-281.

Soucy JP, F Lafaille, P Lemoine, A Mrini and L Descarries (1994) Validation of the transporter ligand cyanoimipramine as a marker of serotonin innervation density in brain. *J. Nucl. Med.* **35**, 1822-1830.

Szechtman H and EZ Woody (2006) Obsessive-compulsive disorder as a disturbance of security motivation: constraints on comorbidity. *Neurotox. Res.* **10**, 103-112.

Towle AG, HE Criswell, EH Maynard, JM Lauder, TH Joh, RA Mueller and GR Breese (1989) Serotonergic innervation of the rat caudate following a neonatal 6-hydroxydopamine lesion: an anatomical, biochemical and pharmacological study. *Pharmacol. Biochem. Behav.* **34**, 367-374.

Ungerstedt U (1971a) Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta Physiol. Scand.* Suppl. **367**, 95.

Ungerstedt U (1971b) Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta Physiol. Scand.* Suppl. **367**, 69.

Ungerstedt U (1971c) Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour. *Acta Physiol. Scand.* Suppl. **367**, 49-68.

Zigmond MJ and EM Stricker (1989) Animal models of parkinsonism using selective neurotoxins: clinical and basic implications. *Int. Rev. Neurobiol.* **31**, 1-79.