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Review

The neonate-6-hydroxydopamine-lesioned rat: a model for clinical neuroscience and neurobiological principles

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Abstract

In 1973, a technique of administering 6-hydroxydopamine (2,4,5-trihydroxyphenylethylamine) intracisternally to neonate rats was introduced to selectively reduce brain dopamine (neonate-lesioned rat). This neonate treatment proved unique when compared to rats lesioned as adults with 6-hydroxydopamine—prompting the discovery of differing functional characteristics resulting from the age at which brain dopamine is reduced. A realization was that neonate-lesioned rats modeled the loss of central dopamine and the increased susceptibility for self-injury in Lesch–Nyhan disease, which allowed identification of drugs useful in treating self-injury in mentally retarded patients. The neonate-lesioned rat has also been proposed to model the hyperactivity observed in attention-deficit hyperactivity disorder. Because the neonate-lesioned rat exhibits enhanced sensitization to repeated NMDA receptor antagonist administration and has functional changes characteristic of schizophrenia, the neonate lesioning is believed to emulate the hypothesized NMDA hypofunction in this psychiatric disorder. Besides modeling features of neurological and psychiatric disorders, important neurobiological concepts emerged from pharmacological studies in the neonate-lesioned rats. One was the discovery of coupling of D_1/D_2-dopamine receptor function. Another was the progressive increase in responsiveness to repeated D_1-dopamine agonist administration referred to as "priming" of D_1-dopamine receptor function. Additionally, a unique profile of signaling protein expression related to neonate reduction of dopamine has been identified. Thus, from modeling characteristics of disease to defining adaptive mechanisms related to neonatal loss of dopamine, the neonate-lesioned rat has had a persisting influence on neuroscience. Despite an extraordinary legacy from studies of the neurobiology of this treatment, a host of unknowns remain that will inspire future investigations.

Theme: Neural basis of behavior
Topic: Neural plasticity

Keywords: Neonate dopamine lesion; 6-Hydroxydopamine; Self-injurious behavior; NMDA hypofunction; Behavioral sensitization; Serotonin hyperinnervation; D_1-dopamine receptors; NMDA receptor antagonists

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Contents

1. Introduction

In 1972, Breese and Traylor [19] lesioned central norepinephrine- and dopamine-containing neurons in the neonatal rat with 6-hydroxydopamine, because this neonatal period is critical for the development of cerebral neurons containing catecholamines. Subsequently, a means was introduced to prevent lesioning of noradrenergic neurons, resulting in a selective reduction of brain dopamine [146]. When behaviors in rats lesioned as adults were compared to those observed in rats lesioned as neonates, differences were observed [22]. While the importance of the consequences of age-dependent lesioning will be reviewed, the unique characteristics observed in the neonate-dopamine deficient animals (neonate-lesioned rat) will be stressed. For example, it will be emphasized how this neonatal treatment has been used to model symptoms and features of developmental, neurological, and psychiatric disorders (see Ref. [15]). Likewise, other distinct characteristics associated with lesioning dopaminergic neurons in immature animals will be described that have elucidated basic neurobiological principles. Further, a description of pharmacological studies will be included that provides evidence for a unique biology associated with these neonate-lesioned rats.

In spite of these important contributions, the biological basis of many functional changes altered by destroying dopaminergic neurons in early development remains obscure. Consequently, the potential remains for future work in the neonate-lesioned rats to extend our understanding of neurobiological functions of the CNS unique to the neonate-lesioned rat. Likewise with future investigations, the biology of the features that allow neonate-lesioned rats to model symptoms of specific disease states should be elucidated. Furthermore, by clarifying the mechanisms responsible for the distinct pharmacology of specific centrally acting drugs in the neonate-lesioned rats, new insights into central function, and in some instances, the basis of therapeutic efficacy of selected drugs, could emerge. Thus, in addition to exploring important contributions from previous investigations of neonate-lesioned rats, this overview will emphasize potential future investigations of this model that may extend our understanding of brain function.

2. Monoamine function in rats lesioned with 6-hydroxydopamine as neonates

After intracisternal administration of 6-hydroxydopamine (100 μg) to immature rats, a marked reduction in both norepinephrine and dopamine levels is observed [19]. A selective reduction of brain dopamine is attained by preventing the action of the 6-hydroxydopamine on noradrenergic neurons [146]. In Fig. 1, an example of the extent of the loss of striatal tyrosine hydroxylase immuno-

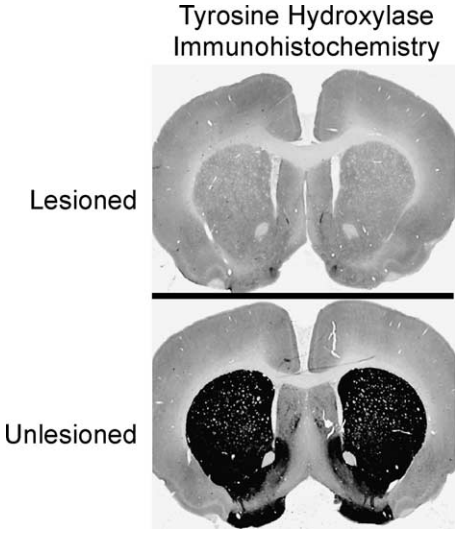

Fig. 1. Tyrosine hydroxylase immunohistochemistry following neonatal treatment with 6-hydroxydopamine. This adult neonate-lesioned rat received desipramine 30 min prior to the administration of 100 μg of 6-hydroxdopamine intracisternally at 3 days of age.

reactivity is provided to illustrate the selective destruction of dopaminergic neurons following 6-hydroxydopamine treatment to neonatal animals. The loss of dopaminergic neurons after neonate lesioning with 6-hydroxydopamine has been the focus of numerous investigations (e.g., Refs. [6,38,56,60,66,89,109,110,123,124]).

Accompanying the loss of dopamine after treating neonate animals with 6-hydroxydopamine is a major increase in striatal serotonin content [12,22,97,120,157]. The degree of this serotonergic hyperinnervation has been carefully delineated as an increase in sprouting of serotonergic neurons [40,58,97,107,125,147,148,157]. This increase in serotonin is not observed in rats lesioned as adults with 6-hydroxydopamine [22]. Based upon these observations, Kostrzewa et al. [97] suggested that the altered serotonergic function in neonate-lesioned animals may contribute to their unique functional characteristics (see below). In spite of the magnitude and reproducibility of the hyperinnervation of serotonin-containing neurons following 6-hydroxydopamine treatments to immature animals, the underlying molecular and physiological basis of this serotonergic hyperinnervation has not been delineated.

3. Behavioral and functional evaluations of neonate-6-hydroxydopamine lesioned rats

Adult rats treated with 6-hydroxydopamine exhibit severe adipsia and aphagia that persists for considerable time after lesioning [17,18,159,161]. While rats lesioned as neonates often exhibit reduced body weight at adulthood [19,146], neonate lesioning of dopaminergic neurons results in less impairment of ingestive behavior and motor function than occurs in rats lesioned as adults [19,37,39,146,164]. Nonetheless, the neonate-lesioned rats do exhibit a persistent deficit in sucrose intake similar to that seen in rats lesioned as adults [146]. In addition to the physical characteristics seen with this model of neonate lesioning of dopaminergic neurons, these lesioned rats exhibit several functional deficiencies upon reaching adulthood (see Refs. [146,164,165]). These lesioned rats have deficits in learning and memory [6,111,141,146,155] and exhibit impaired habituation and alterations in startle responses and sensory gating [134,135,150]. A selective reduction of norepinephrine-containing neurons in brain does not induce the functional changes that follow the developmental loss of dopaminergic neurons [146].

Pharmacological studies in rats lesioned as neonates and those lesioned as adults also revealed functional differences between these treatments following specific dopamine receptor agonist administration. For example, the neonate-lesioned rats are considerably less sensitive to D_2-dopamine receptor agonist-induced locomotion than rats lesioned as adults [25]. In contrast, the neonate-lesioned rats consistently exhibit greater activity to D_1-dopamine agonist administration than adult-lesioned rats [25] (see Fig. 2). Additionally, adult-lesioned rats given a D_2-dopamine receptor antagonist exhibit severe akinesia, whereas at adulthood the neonate-lesioned rats show virtually no motor dysfunction to this receptor blockade [38,60]. The doses of the dopamine receptor antagonists without effect in neonate-lesioned rats produce a near total immobility in non-lesioned rats [60]. These latter pharmacological findings further emphasize the functional differences obtained with the age-dependent lesions. The characteristics of rats lesioned as adults or as neonates have been summarized by Reader and Dewar [132]. Finally, the neonate-lesioned rats display increased oral activity to a D_1-dopamine receptor agonist [93,95] and following chronic haloperidol exposure [82]. This sensitivity to drug-induced oral activity

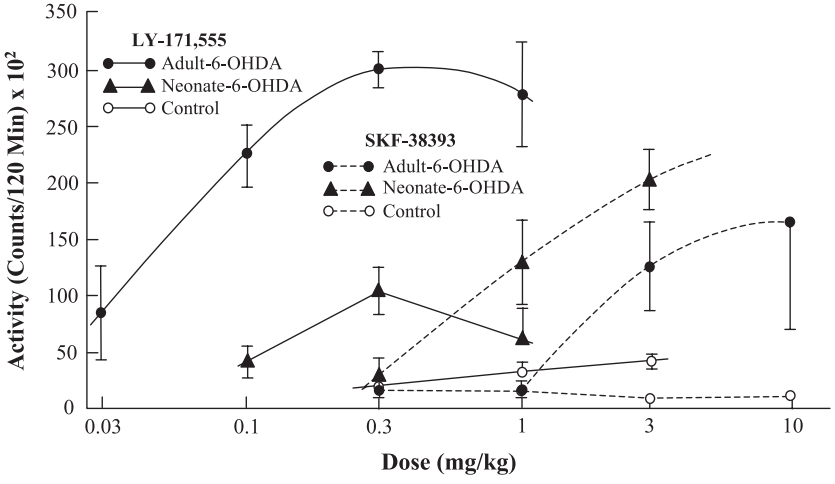

Fig. 2. Dose–response relationships of a D_1-dopamine agonist, SKF-38393, and a D_2-dopamine agonist, LY-171555, in rats lesioned as adults (adult-6-OHDA) or as neonates (neonate-6-OHDA) on locomotor activity. Each value is the mean±S.E.M. of 4–11 rats. The response to all doses of LY-171555 in both the adult and neonate-lesioned rats are significantly different from values in unlesioned control (Control) rats ($p<0.05$). The values for LY-171555 in the neonate-6-OHDA group are significantly different from values in the adult-6-OHDA group ($p<0.001$). The neonate-6-OHDA group exhibited significantly greater locomotor responses to SKF-38393 at the 1- and 3-mg/kg doses compared to responses for this agonist in the adult-6-OHDA rats ($p<0.01$). Modified from Breese et al. [25].

in neonate-lesioned rats requires further attention to assess the relevance of this elevated susceptibility.

4. Modeling self-injurious behavior in the neonate-lesioned rat: relation to Lesch–Nyhan disease

In the early 1970s when our laboratory was lesioning adult rats with 6-hydroxydopamine to emulate the dopamine loss in Parkinsonism [17], we discovered that rats lesioned with 6-hydroxydopamine when immature exhibit self-injurious behavior in response to L-DOPA administration after reaching maturity (see example in Table 1). The doses of L-DOPA that induce self-injury in the neonate-lesioned rats do not induce this behavioral response in rats lesioned as adults [22], an additional differing characteristic dependent upon the age at which dopaminergic neurons are destroyed. Because of the severity of the L-DOPA-induced self-injury, the importance of this observation was not considered further until 1981. At this time, Lloyd et al. [104] reported in the *New England Journal of Medicine* that brain dopamine was drastically reduced in Lesch–Nyhan disease—a genetic disorder caused by a deficiency of hypoxanthine-phosphoribosyl-transferase (HPRT; [101,136]). Subsequently, Wong et al. [168] and Ernst et al. [65], using differing PET procedures, provided confirmation of this loss of dopaminergic neurons in living humans with Lesch–Nyhan disease.

Important to the present discussion is that the Lesch–Nyhan syndrome is characterized by compulsive self-injurious behavior, choreoathetosis, and severe spasticity [101], symptoms dissimilar from those observed in Parkinsonism, where bradykinesia, stooped posture, and tremor are prominent [48]. Further, whereas symptoms of Parkinsonism improve with L-DOPA [48], the symptoms of self-injury and motor dysfunction associated with the Lesch–Nyhan syndrome are reportedly exacerbated following this treatment [86]. The contrasting symptomatology of Parkinsonism and Lesch–Nyhan disease supports the concept that the age at which the dopaminergic neurons are lost contributes to the differing symptoms of these diseases [15,22,23,122]. Based upon evidence that neonate and adult lesioning of dopaminergic neurons also had defining characteristics, the neonate-lesioned rats were proposed to serve as a model of the destruction of dopaminergic neurons in Lesch–Nyhan disease [15,22,23,28,29,31,32], whereas the adult-lesioned rats were to serve as a model of the loss of dopamine associated with Parkinsonism [22,17]. In accord with neonate lesioning relating to the Lesch–Nyhan syndrome, stress increases the sensitization of dopamine receptor agonists to induce self-injury in the neonate-lesioned rats [151], while also exacerbating self-biting and other forms of self-mutilation in Lesch–Nyhan syndrome patients.

Given the relevance of the neonate lesioning to susceptibility for self-injury, it is important to identify neurotransmitter systems that might contribute to this susceptibility. As noted earlier, increased levels of serotonin in the striatum of neonate-lesioned rats and data implicating serotonin in the action of D_1-dopamine receptors [95,97,98] suggest more attention should be given to the potential involvement of this neurotransmitter system in self-injury (see additional discussion below in Section 6). Further, based upon previous work implicating $GABA_A$ receptor function in the substantia nigra reticulata in self-injurious behavior [133], neonate-lesioned rats were found to be more sensitive than unlesioned controls and adult-lesioned rats to the self-injury induced by muscimol microinjected into this brain site [27]. This observation is consistent with the hypothesis that increased $GABA_A$ receptor function in the substantia nigra reticulata contributes to the enhanced susceptibility for self-injury after neonatal lesioning. However, beyond this demonstration of a role for the substantia nigra reticulata in self-injury, other brain regions have not been implicated in the enhanced sensitivity for this behavioral response. Defining various sites in brain relevant to the sensitization of neonate-lesioned rats to self-injury might allow identification of additional neurotransmitter mechanisms that sustain the susceptibility for self-injury. Consequently, making this determination should be a goal of future studies.

Table 1
Incidence of SIB after LY-171555 and SKF-38393 administration to neonate-6-OHDA-treated rats SIB-positive to L-DOPA—an example of coupling of dopamine receptor function*

Treatment	Dose (mg/kg)	Incidence of self-injurious behavior (SIB)	
		No./Total	%
L-DOPA	100	12/12	100
LY-171555	3.0	0/6	0
SKF-38393 (SKF)	1.0	1/12	8
	3.0	2/10	20
	10.0	4/8	50
SKF+LY	1.0+3.0	4/7	57
	3.0+3.0	4/5	80

* All neonate-lesioned animals included in this investigation exhibited self-injury when administered 100 mg/kg of L-DOPA. A dose–response relationship for self-injury was apparent following administration of increasing doses of SKF-38393 (SKF), whereas the maximal dose of LY-171555 (LY) produced no self-injury. When doses of the SKF and LY compounds, which alone produced little or no self-injury, were combined, self-injury was seen in 80% of the lesioned rats. This observation supports the notion of coupling of dopamine receptor subtype function. Self-injury was eliminated by administration of a D_1-dopamine antagonist. Modified from Breese et al. [24].

5. Involvement of dopamine receptor subtypes in L-DOPA-induced self-injury

To examine the involvement of specific dopamine receptor subtypes in the self-injury induced by L-DOPA in neonate-lesioned rats, dose-dependent effects of specific dopamine receptor antagonists were examined. In this respect, it was found that the D_1-dopamine receptor antagonist, SCH-23390, blocked the self-injurious behavior induced by L-DOPA [24,28]. Subsequently, Criswell et al.

[54] examined a variety of D_1-dopamine receptor antagonists and found that all of these compounds reduced the L-DOPA-induced self-injury in the neonate-lesioned rats. Haloperidol, a drug with antagonist actions on D_2-dopamine receptor subtypes, was found to have a partial effect on L-DOPA-induced self-injury [24].

When the dose-dependent effects of selected dopamine receptor subtype agonists [138,158] were assessed [24], a very high dose of a D_1-dopamine receptor agonist produced self-injury in only 50% of the lesioned animals, whereas a D_2-dopamine receptor agonist did not induce this behavioral response (see Table 1; [24]) While this observation, along with the inhibition of self-injury with the D_1-dopamine receptor antagonists, implicated D_1-dopamine receptor function in self-injury, it was not apparent why all animals did not exhibit this behavior after administration of the D_1-dopamine receptor agonist. In order to explore the basis of this lack of effect of the D_1-dopamine receptor agonist to induce maximal expression of self-injury, it was investigated whether D_1- and D_2-dopamine receptors interact to induce self-injury (see Ref. [16]). When a lower dose of the D_1-dopamine receptor agonist, which alone produced limited self-injury, was combined with a D_2-dopamine receptor agonist, which produced no self-injury, self-injury was observed in the majority of the neonate-lesioned rats, as shown in Table 1 [24]. This observation provided behavioral evidence for coupling of D_1-DA and D_2-DA receptor function. Since this early work that identified the coupling of dopamine receptor function [16,24], several observations have supported this concept [85,105,119,149,162].

Consequently, even though a D_2-dopamine receptor agonist does not produce self-injury, an alternative explanation for the limited effect of haloperidol on the self-injury induced by L-DOPA might have been related to its lack of action on other D_2-dopamine-like receptor subtypes (i.e., D_3- and D_4-dopamine receptors). However, haloperidol was found to have similar or greater binding potency on D_3- and D_4-dopamine receptor subtypes, as on D_2-dopamine receptors [7,43,167]. Furthermore, current data indicate that specific blockade of D_3- and D_4-dopamine receptors [7,167] does not prevent dopamine agonist-induced self-injury (Blake and Breese, unpublished data), seemingly dismissing the possibility for a role of these other D_2-dopamine receptor subtypes in self-injury. Collectively, these data provide convincing evidence that the self-injurious behavior induced by L-DOPA in neonate-lesioned rats is primarily linked to activation of D_1-dopamine receptors, with the D_2-dopamine receptor serving a facilitatory role.

6. Evaluation of drugs on self-injury in neonate-lesioned rats: strategy for treating self-injury in Lesch–Nyhan disease and mentally retarded patients

As a model of self-injury in Lesch–Nyhan disease [22,23,28,29,31], it was considered whether testing of drugs against the self-injurious behavior induced by L-DOPA or apomorphine in neonate-lesioned rats would provide a means to identify potential agents for minimizing self-injury in these HPRT-deficient patients. While having only weak effects on D_1-dopamine receptors [43], olanzapine, risperidone, and clozapine inhibited dopamine agonist-induced self-injury in neonate-lesioned rats [5,52,123]. Consistent with the consideration that the neonate-lesion model could identify drugs effective in treating self-injury in Lesch–Nyhan disease [32], risperidone reduced self-injury in a single Lesch–Nyhan patient [4]. In spite of other atypical antipsychotic drugs having been found effective in reducing agonist-induced self-injury in neonate-lesioned rats [5,52,123], published reports of their ability to reduce self-injury and aggressive behavior in Lesch–Nyhan syndrome have not been forthcoming. Regardless, extended clinical trials of any drugs effective in the model are required to verify that the neonate-lesioned rat can serve to identify drugs beneficial in the treatment of self-injury in patients with Lesch–Nyhan disease.

While the initial focus of drug testing on dopamine agonist-induced self-injury in neonate-lesioned rats related to treating this symptom in Lesch–Nyhan disease, a logic considered was that drugs effective in reducing self-injury in the neonate-lesioned rats might also be beneficial in treating self-injury in mentally retarded patients. The observation that the investigational drug SCH-12679 blocked the self-injury induced by L-DOPA in neonate-lesioned rats [30] provided a basis for this logic, because SCH-12679 had previously been shown to diminish self-injury and aggression in developmentally disabled patients [2,62,84]. Therefore, the assumption extended was that atypical antipsychotic drugs that reduced L-DOPA-induced self-injurious behavior in neonate-lesioned rats [5,52,123] could treat self-injury in some mentally retarded patients. In this respect, it has been reported that clozapine, olanzapine, and risperidone reduce self-injury in a portion of mentally retarded individuals [46,68,76,77,118] and in psychotic individuals exhibiting self-injury [45]. The importance of coupling the preclinical science, which defined the atypical antipsychotic drug reduction of self-injury in the neonate-lesioned rats, with the successful clinical treatment of self-injury in the mentally retarded was recognized by an Award for Therapeutics in 2001 from the American Society for Pharmacology and Experimental Therapeutics.

Even though selective D_1-dopamine receptor antagonists reduce the dopamine agonist-induced self-injury in neonate-lesioned rats [24,54], D_1-dopamine receptor antagonists have yet to be thoroughly tested against aggression and self-injury in patient populations. Given the clinical success of atypical antipsychotic drugs in the treatment of self-injury [46,68,76,77,118], the testing of compounds selective for this dopamine receptor subtype would seem logical. This view is particularly reasonable, because, as noted earlier, SCH-12679, which reduced self-injury and aggression in patients [2,62,84], also reduced L-DOPA-induced self-

injury in neonate-lesioned rats by blocking D_1-dopamine receptors [30].

An additional avenue to be explored is whether other neurotransmitter receptor subtypes associated with atypical antipsychotics contribute to their effectiveness to reduce self-injury. Such investigations could lead to additional means for treating self-injury in Lesch–Nyhan disease and mentally retarded patients. For example, in addition to the actions of atypical antipsychotic drugs on dopaminergic receptors, their action on serotonergic receptors [43] may contribute to their effectiveness to minimize self-injury. Therefore, an alternative to be tested is whether the action of atypical antipsychotics on serotonergic receptors [43] plays a significant role in their effectiveness against self-injury in neonate-lesioned rats [5,52,123]. Even though methysergide was shown not to alter the frequency of self-injury induced by L-DOPA [157], it would seem worthy of testing compounds acting on specific serotonin receptor subtypes before calling into question whether a serotonergic mechanism underlies the action of atypical antipsychotic drugs to reduce self-injury [5,123] (see also section on "Adaptation of Neural Elements in Neonate-Lesioned Rats"). Regardless, identification of new data that will explain the action of the atypical antipsychotics on self-injury in neonate-lesioned rats could provide clues for new therapeutic approaches for treating this symptom in Lesch–Nyhan disease and in the mentally retarded.

7. Modeling symptoms of hyperactivity in neonate-lesioned rats: relation to attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) has features of hyperactivity, impulsivity, inattention, and deficits in learning [10,57]. Because the neonate-6-OHDA-lesioned rat is hyperactive between 21 and 45 days of age [64,140], investigators have made use of this characteristic to model the hyperactive behavior of ADHD [57,140]. Further logic for the use of the neonate-lesioned rat as a model of the ADHD involves the learning and memory deficiencies identified in these rats [6,111,141, 146,155]—another feature associated with ADHD [10,57]. In support of the predictive validity of the neonate-lesioned rat as a model for ADHD, the hyperactivity of neonate-lesioned rats is dose-dependently reduced by central stimulants [57,56,78,108,139,141,171] that are effective in alleviating the elevated activity associated with ADHD [10,57]. Furthermore, central stimulants minimize the learning and memory deficiencies observed in this rat model of ADHD [141,169], just as in the clinical syndrome (see Refs. [10,57]).

Even though neonatal lesioning causes a dramatic loss of central dopaminergic neurons [22,146], a specific D_4-dopamine receptor antagonist [171,172], but not a D_2/D_3-dopamine receptor antagonist [171], blocked the hyperactivity induced by dopamine reduction during development [64,140,171–173]. Therefore, the action of the D_4-dopamine receptor antagonist to reduce hyperactivity in the model would seem to implicate a direct involvement of remaining dopamine in the elevated activity in the lesioned rats. In accord with the importance of reducing D_4-dopamine receptor function to minimize hyperactivity in the neonate-lesioned rats, the genetic deletion of the D_4-dopamine receptor also blocked the hyperactive phenotype induced by a developmental loss of dopamine in mice [8]. Consistent with evidence for an involvement of the D_4-dopamine receptor in the hyperactivity in neonate-lesioned rats was the identification of a substantial increase in levels of the D_4-dopamine receptor subtype in the caudate–putamen of these lesioned animals [171,172]. With respect to the potential participation of this dopamine receptor subtype in ADHD, patients with this syndrome reportedly have a high frequency of specific polymorphisms of the D_4-dopamine receptor gene [99].

Dopamine involvement in the action of central stimulants to increase activity was identified in adult-lesioned rats [20,49,50,80,160,161]. A prominent theory exists that serotonin released by central stimulants is responsible for the paradoxical reduction of hyperactivity in ADHD [21,67,81]. In spite of the major increase in striatal serotonin in the neonate-lesioned rats, the extent of serotonergic involvement in the neonate-lesioned hyperactivity [64], or in the reversal of the neonate-lesioned hyperactivity by central stimulants [56], has yet to be fully examined. However, the hyperactivity in neonate-lesioned rats does not appear to involve 5-$HT_{2A/2C}$ receptors because methysergide was not effective in reducing this response [171]. Nonetheless, the potential participation of other serotonin receptor subtypes in the hyperactivity and in the central stimulant reduction of this symptom should receive further attention.

8. Modeling behavioral sensitization to repeated D_1-dopamine receptor agonist treatment in neonate-lesioned rats: relation to sensitization associated with drug abuse

While evaluating the relationship of D_1-dopamine receptors to function in the neonate-lesioned rats, it was discovered that the initial dose of a D_1-dopamine receptor agonist produced little response [25,51,75]. As shown in Fig. 3, additional doses of a D_1-dopamine receptor agonist produce a progressively greater locomotor responsiveness until a maximum is reached that is approximately five times greater than the initial activity evoked by the agonist [25,51,53,75]. This observation has been confirmed by others [74,75,122]. This sensitization to repeated dosing of neonate-lesioned rats with a D_1-dopamine receptor agonist has been termed "priming" [51]. It is emphasized that the D_1-dopamine receptor agonist does not induce this phe-

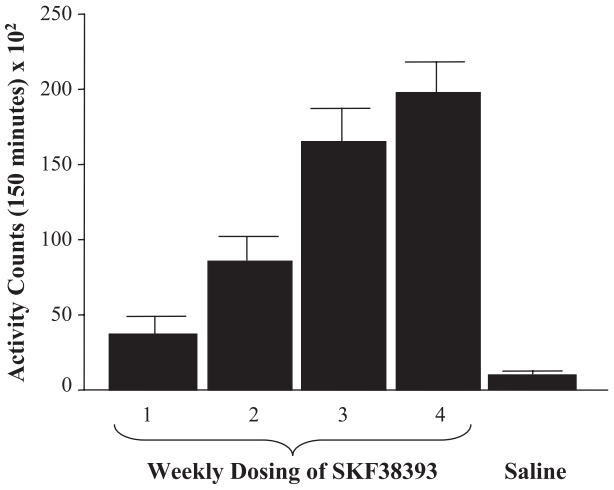

Fig. 3. Sensitization ("priming") of locomotor activity to repeated administration of SKF-38393. These animals had been found to exhibit self-injury to an L-DOPA (100 mg/kg) challenge before receiving repeated 3 mg/kg doses of SKF-38393 at weekly intervals for 4 weeks. The values shown represent the mean±S.E.M. activity counts. The value in control rats was $9.5\pm2.7\times10^2$ activity counts in response to 3 mg/kg of the D_1-dopamine receptor agonist, a value about 1/3 of that seen in the 6-OHDA neonates. A comparable difference was observed between the saline response and the response obtained after priming in the lesioned rats. The increase for the initial three administrations of the agonist differed significantly from each other ($p<0.05$). Modified from Breese et al. [22].

nomenon in unlesioned rats. The D_1-dopamine receptor agonist sensitization phenomenon in the lesioned rats persists for at least 6 months and is not dependent upon the environment in which the sensitizing dose of the agonist is administered [51]. Gong et al. [74] reported that greater D_1-dopamine priming could be obtained if a D_1-dopamine receptor agonist was repeatedly administered before weaning. While repeated administration of a D_2-dopamine receptor agonist does not prime locomotor activity in neonate-lesioned rats [25,42,51], previous repeated treatment with a D_2-dopamine receptor agonist can enhance the locomotor response to a subsequent dose of a D_1-dopamine agonist [25,42,51]. An apparent paradox is that repeated administration of a D_2-dopamine receptor agonist does not increase activity in neonate-lesioned rats [25,42,51], whereas such repeated agonist exposure to intact rats during development increases functional responsiveness [36,94,96]. The means by which the neonate lesioning prevents the increase in responsiveness to repeated D_2-dopamine receptor agonist administration [42,51], while enhancing D_1-dopamine receptor agonist-induced locomotion [25,51], remains unknown. Regardless, the priming of responsiveness to a D_1-dopamine receptor agonist is a unique characteristic of neonate lesioning of dopaminergic neurons. Because of the probable importance of this priming sensitization to symptoms of Lesch–Nyhan disease, the underlying neurobiological basis of the adaptation responsible for this persistent change in behavioral sensitivity needs to be identified.

Thus far, a major clue concerning the adaptation underlying the behavioral sensitization following repeated D_1-dopamine receptor agonist exposure is that pretreatment with an NMDA receptor antagonist prior to each agonist dosing blocks the sensitization (priming) process [53] (Fig. 4). Since previous studies have implicated NMDA receptors in model systems of learning [11,156], the involvement of NMDA receptor function in the priming phenomenon in neonate-lesioned rats suggests this sensitization process by repeated D_1-dopamine agonist administration could be considered to model a type of "neuronal learning" [31,53,128].

In general, priming of neonate-lesioned rats with D_1-dopamine receptor agonists has many characteristics similar to those seen with development of behavioral sensitization following repeated administration of central stimulants [137]. For example, investigations have implicated D_1-dopamine receptors in the sensitization induced by repeated exposure to central stimulants [83,117]. Likewise, pretreatment with an NMDA receptor antagonist reportedly minimizes the sensitization associated with repeated administration of this drug class [90,166], just as NMDA antagonists minimize D_1-dopamine agonist-induced behavioral sensitization in neonate-lesioned rats [53]. Consequently, given these similarities, sensitization with priming by repeated D_1-dopamine receptor agonist administration to neonate-lesioned rats could prove to model the role of D_1-dopamine receptors in the behavioral sensitization associated with multiple exposures to central stimulants.

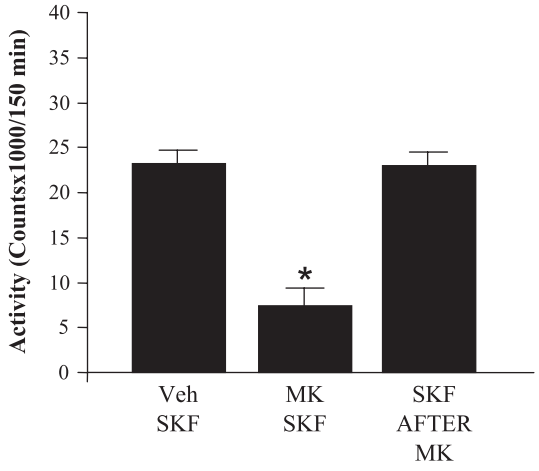

Fig. 4. Blockade of the behavioral response to repeated D_1-DA receptor agonist by pretreatment with the NMDA receptor antagonist (MK-801). Animals were pretreated either with MK-801, 0.3 mg/kg, or vehicle prior to each of four doses of SKF-38393 (3 mg/kg), followed by a final dose of the D_1-DA receptor agonist in the absence of vehicle (VehSKF) or MK-801 (MKSKF). Three additional doses of SKF-38393 (3 mg/kg) were administered after the initial MK-801 treatment (SKF AFTER MK) to demonstrate that the effect of the NMDA antagonist was not permanent. *$p<0.01$ compared to VEHSKF and SKF AFTER MK treatment groups. Modified from Ref. [53].

9. Sensitization of behavioral responsiveness to repeated administration of NMDA receptor antagonists to neonate-lesioned rats

In addition to priming behavioral responsiveness with repeated administration of a D_1-dopamine receptor agonist [25,51], Criswell et al. [55] found that adult neonate-lesioned rats exhibit increased sensitization to MK-801-induced locomotion with repeated administration. Subsequently, as illustrated in Fig. 5, Moy and Breese [121] demonstrated enhanced sensitization of motor activity in neonate-lesioned rats following repeated administration of another NMDA receptor antagonist, phencyclidine (PCP). This response to repeated PCP administration in the neonate lesioned rats is beyond that seen in unlesioned controls [124]. While male rats sensitize to repeated administration of an NMDA receptor antagonist [121], female rats are even more susceptible than the male rats to this enhanced sensitization [121,124]. The basis of this gender difference is unknown. Regardless, such NMDA receptor antagonist sensitization is presumed to be pertinent to the increasing behavioral abnormalities that accompany persistent abuse of PCP and ketamine [14,170]. Importantly, because of the magnitude of the sensitized response to PCP and other NMDA receptor antagonists in neonate-lesioned rats, the identification of specific neural mechanisms responsible for this unique behavioral sensitization process should be facilitated.

The action of MK-801 and PCP in unlesioned rats has been attributed to various monoamine systems [47,106,114,124]. However, extensive reduction of dopamine in the neonate-lesioned rats [22,25,146], as well as

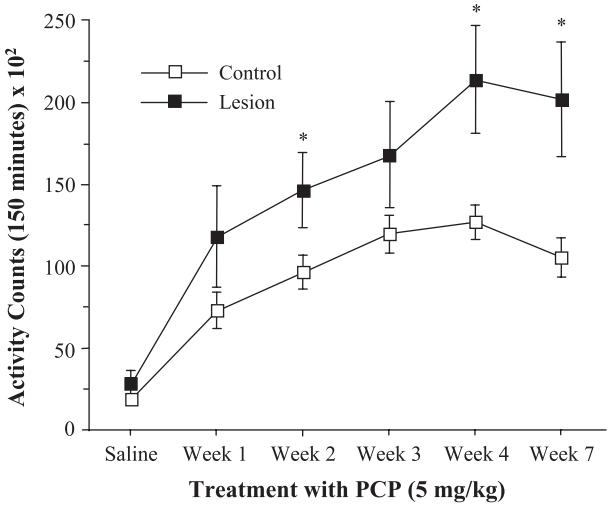

Fig. 5. Sensitization of locomotor activity following repeated exposure to phencyclidine (PCP) in female rats. Data represent the mean±S.E.M. of seven to nine rats in the control and neonate-lesioned (Lesioned) groups repeatedly challenged with PCP (5 mg/kg). Rats were not tested between weeks 4 and 7 to demonstrate the persistence of the sensitization to PCP. *$p<0.05$ compared to the response in the control group. From Moy et al. [124].

administration of haloperidol (0.5 mg/kg) or the D_1-dopamine receptor antagonist, SCH-23390 (0.3 mg/kg) [55,121,124], does not diminish the significant increase in motor activity induced by NMDA receptor antagonists in neonate-lesioned rats. Likewise, the responsiveness to NMDA receptor antagonists is enhanced in animals with depleted monoamines [44,152]. Therefore, the greater responsiveness to PCP after repeated exposure in the neonate-lesioned rats is likely associated with a non-dopaminergic mechanism (see Ref. [34]).

With respect to non-dopaminergic system involvement in the sensitization to PCP and other NMDA antagonists, it has been demonstrated that an increase in central serotonergic tone is linked to NMDA antagonist-induced hypermobility [34,71,114]. In this respect, ketanserin, a 5-$HT_{2A/2C}$ selective receptor antagonist, reduced PCP activation in neonate-lesioned rats [124], implicating 5-HT_2-receptor function in the action of PCP. In agreement with these latter results, Swanson and Schoepp [152] found that ketanserin blocked PCP-induced activity in α-methyl-*p*-tyrosine-treated animals. Whereas a drug selective for the 5-HT_{2C}-receptor subtype was without an effect on PCP-induced activity [79], the selective 5-HT_{2A}-receptor antagonist, M100907, reduced PCP-induced activity in normal animals [71,79,114,116] and diminished PCP-induced antagonism of neuronal NMDA responses [163]. Therefore, the 5-HT_{2A} receptor appears to be the critical serotonin 5-HT_2 receptor subtype involved in the hyperactivity induced by PCP. Nonetheless, a 5-HT_3 receptor antagonist also reverses PCP-induced activity in control mice [71]. Since atypical antipsychotic drugs affect 5-HT_{2A} and 5-HT_3 receptors [43], their action to reduce the sensitized PCP-induced activity in neonate-lesioned rats [124] may depend upon these receptor subtypes. Additionally, a group II metabotropic glutamate receptor agonist also reverses PCP-induced behavior in monoamine-depleted animals [152], a finding that will need integration with results implicating other non-dopaminergic systems in the action of NMDA antagonists.

10. Proposed NMDA hypofunction in neonate-lesioned rats: a model of NMDA hypofunction in schizophrenia?

It is notable that neuropathology of schizophrenia has been linked to a sensitization process [102]. Since schizophrenic patients evidence enhanced susceptibility to the actions of NMDA receptor antagonists [87,100,113], it is possible that the sensitization of symptoms associated with the course of schizophrenia is in some way related to their increased responsiveness to this drug class. This enhanced susceptibility of schizophrenics to NMDA receptor antagonists led to the proposal that a state of NMDA receptor hypofunction is inherent to this disorder [87,88,127]. Therefore, because neonate-lesioned rats exhibit an exacerbated responsiveness to NMDA antagonists, there is a logic

that the neonate-lesioned rats could serve as a model of the NMDA hypofunction in schizophrenia [34,121]. As noted earlier, the neonate-lesioned rats at adulthood also demonstrate abnormalities in habituation, startle responses, and sensory gating [134,135,150], functional deficits which have been previously associated with schizophrenia [69,70,129]. Moreover, just as seen in schizophrenia [33], the neonate-lesioned rats do not up-regulate nicotinic cholinergic receptors after chronic nicotine exposure (Charles R. Breese, personal communication). Therefore, the neonate-lesioned rat may be a valuable model to extend our understanding of the neural basis of the enhanced responsiveness to NMDA-receptor antagonists in some forms of schizophrenia [87,88,100,112,113].

Of potential relevance to neonate-lesioned rats modeling NMDA hypofunction in schizophrenia is the finding that the atypical antipsychotic drugs, olanzapine and clozapine, reduce the sensitized action of the NMDA receptor antagonist PCP in the lesioned rats [34,121,124]. In contrast, haloperidol does not reduce this acute sensitized behavioral response to PCP [121,124]. Consistent with these findings, a greater efficacy of atypical antipsychotic compounds, in comparison to haloperidol, has also been reported for PCP-induced locomotion [71], social withdrawal [47], deficits in prepulse inhibition (see Refs. [70,103]), and changes in neural activity [126,163] in normal animals. In addition, it is notable that clozapine [112], but not haloperidol [100], reduces the cognitive and psychotomimetic impact of the NMDA receptor antagonist, ketamine, in schizophrenics. It would be of considerable interest to know whether acute treatment with antipsychotic drugs reverses deficits in sensory gating observed in neonate-lesioned rats.

Because acute administration of atypical antipsychotic drugs minimizes sensitized responses to PCP in neonate-lesioned rats, a question that can be raised is whether this response to NMDA receptor antagonists provides a means to screen for agents with potential therapeutic usefulness in the treatment of schizophrenia. Despite the fact that atypical antipsychotic drugs interact with 5-HT_2 receptor subtypes and with 5-HT_3 receptors [43] and drugs specific for these serotonergic receptors reduce the action of NMDA receptor antagonists [71,79,114,116], it has not been carefully defined whether agents selective for these specific serotonergic receptor subtypes are useful in treating specific symptoms of schizophrenia (see Ref. [130])—another area for future investigation.

It is held that chronic administration of antipsychotic drugs is needed to attain full benefit of antipsychotic treatment of schizophrenic symptoms [9]. In this respect, prolonged treatment with olanzapine, prevents the sensitization induced by repeated PCP administration, whereas haloperidol is without an effect [124]. Clearly, the differing consequences of chronic treatment with typical and atypical antipsychotic drugs on responsiveness to NMDA receptor antagonists suggest that adaptive change induced by typical antipsychotics is not equivalent to that adaptation induced by atypical antipsychotic drugs. Therefore, defining the basis of the difference between chronic administration of typical and atypical antipsychotic drugs to block NMDA receptor antagonist sensitization would seem worthy of future attention. Importantly, the persistent action of chronic olanzapine, but not haloperidol, to minimize the induction of sensitization by repeated NMDA receptor antagonist exposure [124] may be relevant to treating the worsening (sensitization) symptoms associated with schizophrenia over an extended course of the disease.

11. Adaptation of neural elements in neonate-lesioned rats

Despite sensitization with priming of D_1-dopamine receptor function [51], neonatal lesions do not alter D_1-dopamine receptor binding [26,59–61,75,110,142,171] or mRNA for the D_1-dopamine receptor in the striatum [61]. Furthermore, the behavioral sensitization process following repeated administration of a D_1-dopamine receptor agonist is not associated with an increase in adenylyl cyclase by D_1-dopamine receptor activation [142]. Likewise, Luthman et al. [110] did not find a change in striatal DARPP-32 (dopamine and cAMP regulated phosphoprotein-32) immunoreactivity in neonate-lesioned rats. While acute administration of a D_1-dopamine receptor agonist to neonate-lesioned rats evokes a major increase in Fos-like immunoreactivity in the striatum compared to control, previous agonist exposure (priming) of the neonate-lesioned rats does not affect the magnitude of this change in Fos to a subsequent D_1-dopamine receptor agonist challenge [89]. Therefore, it remains a paradox why direct measures of D_1-dopamine receptor function in the striatum do not reflect the enhanced behavioral sensitization associated with D_1-dopamine agonist priming. Nonetheless, enhanced behavioral responsiveness is observed following intracerebral microinjections of D_1-dopamine receptor agonists into the nucleus accumbens and dorsal striatum of neonate-lesioned rats [26].

Most investigations have not reported a change in D_2-dopamine receptor binding in the striatum of neonate-lesioned rats [26,60,95,142]. On the other hand, using the radiolabelled ligand, raclopride, Dewar et al. [59] reported a small increase in striatal D_2-dopamine receptors—a finding confirmed by Huang et al. [82]. Likewise, Zhang et al. [171] found a small increase in D_2-like receptor binding in neonate-lesioned rats when utilizing radiolabelled nemonapride. Similar to that seen in control rats, Huang et al. [82] demonstrated that increased raclopride binding in neonate-lesioned rats accompanied chronic haloperidol treatment; however, this increased raclopride binding in the striatum of the lesioned rats returned to baseline levels after withdrawal from the chronic haloperidol exposure. The mRNA for the D_{2L}-dopamine receptor was also elevated in neonate-

lesioned rats by chronic haloperidol treatment—a change that also returned to baseline levels upon removal of the haloperidol [82]. In contrast to these latter findings, Duncan et al. [60] found that chronic haloperidol did not elevate D_2-dopamine receptor binding in neonate-lesioned rats. Likewise, chronic SCH23390, a D_1-dopamine receptor antagonist, did not alter D_1-dopamine receptor binding in the developmentally lesioned animals [60]. Chronic treatment with both dopamine receptor antagonists increased binding in control rats and in rats lesioned as adults [60].

There are reports that serotonergic mechanisms contribute to the D_1-dopamine agonist-induced supersensitivity in neonatal-lesioned rats [3,41,73,95]. In this respect, Kostrzewa et al. [95] implicated a serotonergic mechanism involving the 5-HT_{2C} receptor in the oral activity induced by SKF-38393, an observation that could be relevant to atypical antipsychotic action to reduce D_1-dopamine agonist-induced activity in neonate-lesioned rats [123] and to minimize their susceptibility for self-injury [5,52]. Methysergide minimizes L-DOPA-induced sniffing and reduces paw treading and rearing induced by a D_1-dopamine agonist in neonate-lesioned rats [157]. Further evidence that serotonergic mechanisms interact with D_1-dopamine receptor action is that targeted behaviors induced by D_1-dopamine agonist administration to neonate-lesioned rats are blocked by lesioning with 5,7-dihydroxytryptamine to reduce serotonin [3,41] or by administration of 5$HT_{2A/2C}$ antagonists to reduce 5-HT_2 receptor function [3,95]. In respect to D_1-dopamine receptor agonist priming, Papadeas et al. [128] found that administration of ketanserin, a 5-$HT_{2A/2C}$ receptor antagonist, prior to each repeated dosing of a D_1-dopamine receptor agonist to neonate-lesioned rats, prevented behavioral sensitization. Furthermore, Bishop et al. [13] reported that DOI [(−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl], a selective 5-$HT_{2A/2C}$-receptor agonist, induced motor activity in neonate-lesioned rats when microinjected into the striatum. This response to DOI was blocked by a 5-HT_{2A}, but not by a 5-HT_{2C} receptor antagonist [13]. Consequently, data suggest that an adaptation of serotonergic mechanisms may contribute to the unique characteristic of neonate-lesioned rats to have increased sensitivity to D_1-dopamine receptor agonists. Nonetheless, because of ambiguity concerning the means by which specific serotonin receptor subtypes contribute to D_1-dopamine receptor sensitization, this area of neonate-lesioned neurobiology should receive additional scrutiny.

Accompanying the robust striatal serotonergic hyperinnervation in the neonate-lesioned rats [12,22,107,147,148,157] is an increase in striatal 5-HT receptors, with the greatest elevation observed in 5-HT_2 receptor subtypes [131]. In support of altered serotonergic mechanisms in neonate-lesioned rats, *m*-CPP (*meta*-chlorophenylpiperazine), a compound presumed to act on 5-HT_{2C} receptors, reportedly enhances chewing, oral activity, head-nodding, and self-biting, after this lesion [3,72,93,95]. el Mansari et al. [63] demonstrated that striatal neurons in neonate-lesioned rats exhibited increased responsiveness to *m*-CPP and DOI, a change not observed in rats lesioned with 6-hydroxydopamine as adults [63]. This latter observation provides additional evidence for the differing functional profiles depending upon the age at which dopaminergic neurons are destroyed. The response pattern to *m*-CPP in neonate-lesioned rats is not reduced by ketanserin [72], but has been shown to be minimized by mianserin [72,95]. Additionally, Allen and Davis [3] reported a reduction of *m*-CPP responsiveness by mianserin in neonate-lesioned animals with serotonergic neurons destroyed with 5,7-dihydroxytryptamine. The neural adaptation in the neonate-lesioned rats responsible for *m*-CPP-induced sensitization of behavioral and electrophysiological responsiveness is unknown, but could relate to the increase in 5-HT_2 receptors in these animals [131].

A number of neuropeptides have been found to change in the neonate-lesioned rats. For example, the level of striatal substance P is reduced by the neonate lesion [109,143,144], but is not reduced in rats lesioned as adults [144]. Nonetheless, the presence of the patchy distribution of substance P and the distribution of enkephalin to the matrix persists following the neonate lesion [153]. On the other hand, met-enkephalin content is increased in both adult and neonate-lesioned groups [144,145]. Upon exposure to L-DOPA, substance P is decreased further in the neonate-lesioned animals, whereas the elevation of enkephalin is further increased [143]. While a unilateral lesion to dopaminergic neurons in neonate rats increases striatal neuropeptide Y, a similar increase is also observed in rats given this lesion as adults [1]. The level of this peptide in the bilaterally neonate-lesioned rats has not been determined. Luthman et al. [109] observed a reduction of cholecystokinin levels in the nucleus accumbens and reduced neurotensin content in the ventral mesencephalon of rats lesioned during development with 6-hydroxydopamine. Furthermore, long-term neural adaptation in neonate-lesioned rats is evidenced by persistent changes in other stimulus-responsive proteins. Utilizing immunohistochemistry, FosB was found elevated in the striatum at adulthood in the neonate-lesioned rats without previous priming with a D_1-dopamine receptor agonist [91]. It has also been discovered that COX-2 is elevated in the striatum weeks after the neonate lesioning [91]. Whether there is a persistent change in COX-2 in the brain of adult-lesioned rats after lesioning has not been determined.

A remarkable biochemical change recently observed in neonate-lesioned rats after behavioral sensitization with repeated dosing with a D_1-dopamine receptor agonist is an increase in phosphorylated extracellular signal-regulated kinase (p-ERK) immunoreactivity, which was primarily present in layers 2/3 of the medial prefrontal cortex, 7 days after the final repeated exposure to the agonist [128]. This persistent change gradually declined, but remained significantly elevated 36 days after the priming with the D_1-dopamine receptor agonist [128]. An illustration denoting

the magnitude of this change in p-ERK immunoreactivity in the medial prefrontal cortex of a primed neonate-lesioned rat versus one that did not receive repeated agonist exposure is shown in Fig. 6. Repeated administration of the D_1-dopamine receptor agonist to unlesioned animals did not result in a persistent increase in the expression of p-ERK immunoreactivity in the prefrontal cortex [128]. An additional noteworthy finding was that a persistent increase in the immunoreactivity for phosphorylated cAMP response element-binding protein (p-CREB) accompanied the persistent change in p-ERK immunostaining associated with priming [128]. A particularly important aspect of these initial findings is the fact that persistent changes in p-ERK and p-CREB immunoreactivity observed in the medial prefrontal cortex are not present in the striatum or nucleus accumbens after priming [128]. This latter finding in brain of neonate-lesioned rats illustrates the regional selectivity for the adaptive changes in these signaling proteins after repeated D_1-dopamine receptor agonist administration. Finally, just as an NMDA receptor antagonist blocks the behavioral sensitization following repeated administration of a D_1-dopamine receptor agonist [51], the adaptive change in the prefrontal cortex responsible for the persistent increase in p-ERK immunoreactivity induced by the priming procedure is also minimized by antagonism of NMDA receptors [128]. While ketanserin minimized behavioral priming, it is curious that this 5-$HT_{2A/2C}$-receptor antagonist did not reduce the persistent increase in p-ERK immunoreactivity induced by repeated D_1-dopamine receptor agonist administration [128]. These data would seem to discount a role for p-ERK in the behavioral sensitization induced by priming. Consequently, the role of the persistent increase in the signaling factors in the prefrontal cortex of the primed neonate-lesioned rat is currently being explored.

Some adaptive changes after neonate lesioning are obviously related to the loss of dopaminergic neurons in the immature rat (e.g., the increase in striatal serotonin and the expression of selected proteins in the striatum). However, there are other adaptive changes associated with repeated exposure to a D_1-dopamine receptor agonist in the neonate-lesioned rats. For example, repeated dosing with a D_1-dopamine agonist enhances the locomotor response to scopolamine administration [53] and pilocarpine responsiveness is increased in neonate-lesioned rats [92]. Nonetheless, the possible involvement of cellular and molecular events responsible for the specific cholinergic receptor mechanisms that account for these unique response characteristics in neonate-lesioned rats has not been adequately explored. Another area that has been neglected is definition of the functional consequences of the neuropeptide changes observed in the neonate-lesioned rats. Identification of the role these peptides play in the adaptive changes in the neonate-lesioned rats would likely provide a new understanding of brain function. Given the distinct functional changes seen with lesioning dopaminergic neurons at differing ages, it would be particularly important to determine if such persistent changes in peptides and proteins in neonate-lesioned animals (with or without priming) occur in rats in which there is a bilateral destruction of striatal dopaminergic neurons during adulthood.

12. Future directions

Defining the mechanisms accounting for the various changes observed after lesioning dopaminergic neurons during development has considerable potential for inspiring future studies. Certainly, such an effort will provide a better understanding of the neurobiology of brain function. Further, identifying the neurobiological foundation of the unique features of neonate-lesioned rats should provide insight into the basis of neurological and psychiatric symptoms that are emulated by the model.

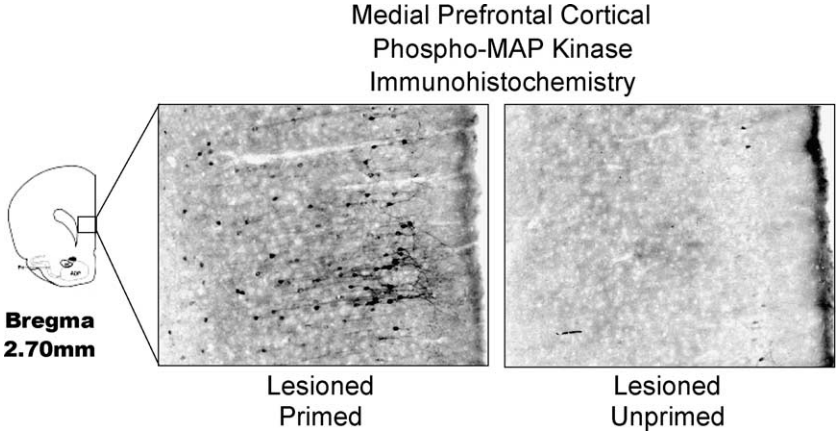

Fig. 6. Increased expression of p-ERK (phospho-MAP kinase) immunoreactivity in the prefrontal cortex of neonate-lesioned rats 7 days after priming doses of the D_1-dopamine receptor agonist. For priming, the rats received a single 6-mg/kg dose followed by two 3-mg/kg doses of SKF-38393 at weekly intervals. p-ERK immunoreactivity increased in the rats that received multiple doses of the D_1-dopamine receptor agonist, but not in the lesioned animals that received vehicle. A single 3-mg/kg dose did not increase expression of p-ERK at 7 days. (Confirmation of data in Ref. [128]).

From a basic neurobiological perspective, the hyper-innnervation of serotonergic neurons in the striatum after the neonatal lesion could serve as a fertile area of future research to define the neurobiological basis of this neural outgrowth, as well as to facilitate an understanding of the potential interaction of neurotransmitter systems that contribute to the normal control of serotonin innervation of the striatum during development. Likewise, the role of serotonergic receptor function in the priming of behavioral and biochemical changes in the neonate-lesioned rat by repeated D_1-dopamine receptor agonist should be explored further.

Inhibition of the increased susceptibility of the neonate-lesioned rat to self-injury induced by dopamine agonists has proven to be a useful means for identifying drug groups that minimize this behavior in patient populations. Therefore, it would seem a worthy pursuit to determine whether other drug classes can be identified that will minimize the self-destructive behavior and aggression induced by general dopamine receptor agonists in these neonate-lesioned rats. This effort could conceivably result in the discovery of drugs with similar therapeutic efficacy as the atypical antipsychotics currently used for this purpose, but with fewer side effects. Further, such information may identify an underlying cause for the increased susceptibility of neonate-lesioned rats to L-DOPA-induced self-injury, information that should be directly relevant to Lesch–Nyhan disease.

Investigations concerning behavioral sensitization by repeated D_1-dopamine receptor agonist administration in neonate-lesioned rats should include determining whether additional biochemical changes distinct from p-ERK and p-CREB can be delineated—defining in each case the sites in brain where these changes are found. Identification of such transcriptional changes in future experiments should provide a definitive understanding of the permanence of behavioral responses following priming of D_1-dopamine receptor function. Further, such results are likely to have implications for identifying mechanisms that support the behavioral sensitization that accompanies repeated central stimulant exposure, for identifying the basis of symptoms in a disorder like Lesch–Nyhan disease, and for providing clues about fundamental aspects of memory consolidation.

Just as investigating the sensitization to repeated administration of D_1-dopamine receptor agonists in the neonate-lesioned rats has potential importance to neurobiology, so too does defining the behavioral sensitization induced by repeated NMDA receptor antagonists to neonate-lesioned rats. The enhanced responsiveness to NMDA receptor antagonists as well as the selective abnormalities in the neonate-lesioned rat that are common with those in schizophrenia suggest that neural mechanism(s) responsible for features linked to the NMDA hypofunction observed in schizophrenia can be elucidated with the model. Based upon previous pharmacological studies implicating serotonergic and mGLU (metabotropic glutamate) receptors in the action of NMDA receptor antagonists, the contribution of these receptor systems and their signaling pathways could help elucidate the mechanisms responsible for the sensitization process induced by repeated administration of NMDA receptor antagonists; therefore, this area needs careful scrutiny. As noted earlier, this particular field of research could have importance for understanding the course of worsening symptoms in schizophrenia, a process attributed to sensitization [102].

Masuo et al. [115] examined the gene expression profile seen in the striatum and midbrain of young adult rats lesioned as neonates with 6-hydroxydopamine and found a variety of gene alterations. This investigation did not include neonate-lesioned rats repeatedly treated with a D_1-dopamine receptor agonist. Thus, this important approach should be applied to defining genes in selected brain regions, such as the striatum and the prefrontal cortex, in neonate-lesioned rats with and without priming with a D_1-dopamine receptor agonist. These results can be compared to those obtained in controls and rats lesioned with 6-hydroxydopamine as adults. This effort can be expected to extend our understanding of the unique properties of the neonate-lesioned rats. Given the importance of knockout technology to investigate neural mechanisms, it is unfortunate that it has been difficult to maintain viable mice administered 6-hydroxydopamine during development ([35]; Breese, unpublished data). Likewise, dopamine-deficient mice with selective inactivation of tyrosine hydroxylase did not survive unless given L-DOPA to restore dopamine function [154]. In spite of these earlier observations, there is a report that mice administered 6-hydroxydopamine intracerebroventricularly during development can survive [8]. Thus, given this latter result [8], it is promising that future experiments in "knockout" mice with neonatal 6-hydroxydopamine lesioning will allow this type of gene technology to be used to explore the underlying gene components responsible for the functional consequences of dopamine loss during development.

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References

[1] D.N. Abrous, M. Le Moal, J.P. Herman, The increase in striatal neuropeptide Y immunoreactivity induced by neonatal dopamine-depleting lesions in rats is reversed by intrastriatal dopamine-rich transplants, Brain Res. 656 (1994) 169–173.
[2] J.-M. Albert, R. Elie, S.F. Cooper, A. Clermont, Y. Langlois, Efficacy of SCH-12679 in the management of aggressive mental retardates, Curr. Ther. Res. 221 (1977) 786–795.
[3] S.M. Allen, W.M. Davis, Relationship of dopamine to serotonin in the neonatal 6-OHDA rat model of Lesch–Nyhan syndrome, Behav. Pharmacol. 10 (1999) 467–474.

[4] S.M. Allen, S.N. Rice, Risperidone antagonism of self-mutilation in a Lesch–Nyhan patient, Prog. Neuro-psychopharmacol. Biol. Psychiatry 20 (1996) 793–800.
[5] S.M. Allen, J.N. Freeman, W.M. Davis, Evaluation of risperidone in the neonatal 6-hydroxydopamine model of Lesch–Nyhan syndrome, Pharmacol. Biochem. Behav. 59 (1998) 327–330.
[6] T. Archer, W. Danysz, A. Fredriksson, G. Jonsson, J. Luthman, E. Sundstrom, A. Teiling, Neonatal 6-hydroxydopamine-induced dopamine depletions: motor activity and performance in maze learning, Pharmacol. Biochem. Behav. 31 (1988) 357–364.
[7] V. Audinot, A. Newman-Tancredi, A. Gobert, J.M. Rivet, M. Brocco, F. Lejeune, L. Gluck, I. Desposte, K. Bervoets, A. Dekeyne, M.J. Millan, A comparative in vitro and in vivo pharmacological characterization of the novel dopamine D3 receptor antagonists (+)-S 14297, nafadotride, GR 103,691 and U 99194, J. Pharmacol. Exp. Ther. 287 (1998) 187–197.
[8] M.E. Avale, T.L. Falzone, D.M. Gelman, M.J. Low, D.K. Grandy, M. Rubinstein, The dopamine D4 receptor is essential for hyperactivity and impaired behavioral inhibition in a mouse model of attention deficit/hyperactivity disorder, Mol. Psychiatry. 9 (2004) 718–726.
[9] R.J. Baldessarini, Drugs and the treatment of psychiatric disorders, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 1990, pp. 383–435.
[10] R.A. Barkley, Attention-deficit hyperactivity disorder, Sci. Am. 279 (1998) 66–71.
[11] C.A. Barnes, Spatial learning and memory processes: the search for their neurobiological mechanisms in the rat, Trends Neurosci. 11 (1988) 163–169.
[12] T.W. Berger, S. Kaul, E.M. Stricker, M.J. Zigmond, Hyperinnervation of the striatum by dorsal raphe afferents after dopamine-depleting brain lesions in neonatal rats, Brain Res. 336 (1985) 354–358.
[13] C. Bishop, J.L. Tessmer, T. Ullrich, K.C. Rice, P.D. Walker, Serotonin 5-HT2A receptors underlie increased motor behaviors induced in dopamine-depleted rats by intrastriatal 5-HT2A/2C agonism, J. Pharmacol. Exp. Ther. 310 (2004) 687–694.
[14] W.V. Bobo, S.C. Miller, Ketamine as a preferred substance of abuse, Am. J. Addict. 11 (2002) 332–334.
[15] C.R. Breese, G.R. Breese, Use of neurotoxins to destroy catecholamine-containing neurons in neonatal and adult animals to model clinical disorders: approach for defining adaptive neural mechanisms and role of neurotrophic factors in brain, Highly Selective Neurotoxins: Basic and Clinical Applications, 1997, pp. 19–73.
[16] G.R. Breese, R.A. Mueller, SCH-23390 antagonism of a D-2 dopamine agonist depends upon catecholaminergic neurons, Eur. J. Pharmacol. 113 (1985) 109–114.
[17] G.R. Breese, T.D. Traylor, Effect of 6-hydroxydopamine on brain norepinephrine and dopamine evidence for selective degeneration of catecholamine neurons, J. Pharmacol. Exp. Ther. 174 (1970) 413–420.
[18] G.R. Breese, T.D. Traylor, Depletion of brain noradrenaline and dopamine by 6-hydroxydopamine, Br. J. Pharmacol. 42 (1971) 88–99.
[19] G.R. Breese, T.D. Traylor, Developmental characteristics of brain catecholamines and tyrosine hydroxylase in the rat: effects of 6-hydroxydopamine, Br. J. Pharmacol. 44 (1972) 210–222.
[20] G.R. Breese, B.R. Cooper, R.D. Smith, Biochemical and behavioral alterations following 6-hydroxydopamine administration into brain, in: E. Usdin, S. Snyder (Eds.), Frontiers in Catecholamine Research, Pergamon, 1973, pp. 701–706.
[21] G.R. Breese, B.R. Cooper, A.S. Hollister, Involvement of brain monoamines in the stimulant and paradoxical inhibitory effects of methylphenidate, Psychopharmacologia 44 (1975) 5–10.
[22] G.R. Breese, A.A. Baumeister, T.J. McCown, S.G. Emerick, G.D. Frye, K. Crotty, R.A. Mueller, Behavioral 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 (1984) 343–354.
[23] G.R. Breese, A.A. Baumeister, T.J. McCown, S.G. Emerick, G.D. Frye, R.A. Mueller, Neonatal-6-hydroxydopamine treatment: model of susceptibility for self-mutilation in the Lesch–Nyhan syndrome, Pharmacol. Biochem. Behav. 21 (1984) 459–461.
[24] G.R. Breese, A. Baumeister, T.C. Napier, G.D. Frye, R.A. Mueller, 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 (1985) 287–295.
[25] G.R. Breese, T.C. Napier, R.A. Mueller, 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 (1985) 447–455.
[26] G.R. Breese, G.E. Duncan, T.C. Napier, S.C. Bondy, L.C. Iorio, R.A. Mueller, 6-Hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D1- and D2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding, J. Pharmacol. Exp. Ther. 240 (1987) 167–176.
[27] G.R. Breese, K.L. Hulebak, T.C. Napier, A. Baumeister, G. Frye, R.A. Mueller, Enhanced muscimol-induced behavioral responses after 6-OHDA lesions: relevance to susceptibility for self-mutilation behavior in neonatally lesioned rats, Psychopharmacology (Berl) 91 (1987) 356–362.
[28] G.R. Breese, H.E. Criswell, R.A. Mueller, Evidence that lack of brain dopamine during development can increase the susceptibility for aggression and self-injurious behavior by influencing D1-dopamine receptor function, Prog. Neuro-psychopharmacol. Biol. Psychiatry 14 (1990) S65–S80 (Suppl).
[29] G.R. Breese, H.E. Criswell, G.E. Duncan, R.A. Mueller, A dopamine deficiency model of Lesch–Nyhan disease—the neonatal-6-OHDA-lesioned rat, Brain Res. Bull. 25 (1990) 477–484.
[30] G.R. Breese, H.E. Criswell, R.J. McQuade, R.A. Mueller, L.C. Iorio, Pharmacological evaluation of SCH-12679: evidence for in vivo antagonism of D2 dopamine receptors, J. Pharmacol. Exp. Ther. 252 (1990) 558–567.
[31] G.R. Breese, H.E. Criswell, K.B. Johnson, J.P. O'Callaghan, G.E. Duncan, K.F. Jensen, P.E. Simson, R.A. Mueller, Neonatal destruction of dopaminergic neurons, Neurotoxicology 15 (1994) 149–159.
[32] G.R. Breese, H.E. Criswell, G.E. Duncan, S.S. Moy, K.B. Johnson, D.F. Wong, R.A. Mueller, Model for reduced brain dopamine in Lesch–Nyhan syndrome and the mentally retarded: neurobiology of neonatal-6-hydroxydopamine lesioned rats, Ment. Retard. Dev. Disabil. Res. Rev. 1 (1995) 111–119.
[33] C.R. Breese, M.J. Lee, C.E. Adams, B. Sullivan, J. Logel, K.M. Gillen, M.J. Marks, A.C. Collins, S. Leonard, Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia, Neuropsychopharmacology 23 (2000) 351–364.
[34] G.R. Breese, D.J. Knapp, S.S. Moy, Integrative role for serotonergic and glutamatergic receptor mechanisms in the action of NMDA antagonists: potential relationships to antipsychotic drug actions on NMDA antagonist responsiveness, Neurosci. Biobehav. Rev. 26 (2002) 441–455.
[35] M.D. Brot, M.S. Szczypka, R. Reavell, B.T. Marck, A.M. Matsumoto, R.D. Palmiter, Neonatal 6-hydroxydopamine administration to mice is fatal, Dev. Neurosci. 24 (2002) 531–538.
[36] R.W. Brown, K.D. Thompson, K.N. Thompson, J.J. Ward, S.K. Thacker, M.T. Williams, R.M. Kostrzewa, Adulthood nicotine treatment alleviates behavioural impairments in rats neonatally treated with quinpirole: possible roles of acetylcholine function and neurotrophic factor expression, Eur. J. Neurosci. 19 (2004) 1634–1642.

[37] J.P. Bruno, A.M. Snyder, E.M. Stricker, Effect of dopamine-depleting brain lesions on suckling and weaning in rats, Behav. Neurosci. 98 (1984) 156–161.
[38] J.P. Bruno, E.M. Stricker, M.J. Zigmond, Rats given dopamine-depleting brain lesions as neonates are subsensitive to dopaminergic antagonists as adults, Behav. Neurosci. 99 (1985) 771–775.
[39] J.P. Bruno, M.J. Zigmond, E.M. Stricker, Rats given dopamine-depleting brain lesions as neonates do not respond to acute homeostatic imbalances as adults, Behav. Neurosci. 100 (1986) 125–128.
[40] J.P. Bruno, D. Jackson, M.J. Zigmond, E.M. Stricker, Effect of dopamine-depleting brain lesions in rat pups: role of striatal serotonergic neurons in behavior, Behav. Neurosci. 101 (1987) 806–811.
[41] R. Brus, R.M. Kostrzewa, P. Nowak, K.W. Perry, 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 (1994) 231–237.
[42] R. Brus, R.M. Kostrzewa, P. Nowak, K.W. Perry, J.P. Kostrzewa, Ontogenetic quinpirole treatments fail to prime D2 agonist-enhancement of locomotor activity in 6-hydroxydopamine-lesioned rats, Neurotoxicol. Res. (2003) 329–338.
[43] F.P. Bymaster, D.O. Calligaro, J.F. Falcone, R.D. Marsh, N.A. Moore, N.C. Tye, P. Seeman, D.T. Wong, Radioreceptor binding profile of the atypical antipsychotic olanzapine, Neuropsychopharmacology 14 (1996) 87–96.
[44] M. Carlsson, A. Carlsson, The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice, J. Neural Transm. 75 (1989) 221–226.
[45] K.N. Chengappa, T. Ebeling, J.S. Kang, J. Levine, H. Parepally, Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder, J. Clin. Psychiatry 60 (1999) 477–484.
[46] S.A. Cohen, M.T. Underwood, The use of clozapine in a mentally retarded and aggressive population, J. Clin. Psychiatry 55 (1994) 440–444.
[47] R. Corbett, F. Camacho, A.T. Woods, L.L. Kerman, R.J. Fishkin, K. Brooks, R.W. Dunn, Antipsychotic agents antagonize non-competitive *N*-methyl-D-aspartate antagonist-induced behaviors, Psychopharmacology (Berl) 120 (1995) 67–74.
[48] G.C. Cotzias, P.S. Papavasiliou, R. Gellene, Experimental treatment of parkinsonism with L-Dopa, Neurology 18 (1968) 276–277.
[49] I. Creese, S.D. Iversen, Amphetamine response in rat after dopamine neurone destruction, Nat. New Biol. 238 (1972) 247–248.
[50] I. Creese, S.D. Iversen, Blockage of amphetamine induced motor stimulation and stereotypy in the adult rat following neonatal treatment with 6-hydroxydopamine, Brain Res. 55 (1973) 369–382.
[51] H. Criswell, R.A. Mueller, G.R. Breese, Priming of D1-dopamine receptor responses: long-lasting behavioral supersensitivity to a D1-dopamine agonist following repeated administration to neonatal 6-OHDA-lesioned rats, J. Neurosci. 9 (1989) 125–133.
[52] H.E. Criswell, R.A. Mueller, G.R. Breese, Clozapine antagonism of D-1 and D-2 dopamine receptor-mediated behaviors, Eur. J. Pharmacol. 159 (1989) 141–147.
[53] H.E. Criswell, R.A. Mueller, G.R. Breese, Long-term D1-dopamine receptor sensitization in neonatal 6-OHDA-lesioned rats is blocked by an NMDA antagonist, Brain Res. 512 (1990) 284–290.
[54] H.E. Criswell, R.A. Mueller, G.R. Breese, Pharmacologic evaluation of SCH-39166, A-69024, NO-0756, and SCH-23390 in neonatal-6-OHDA-lesioned rats. Further evidence that self-mutilatory behavior induced by L-dopa is related to D1 dopamine receptors, Neuropsychopharmacology 7 (1992) 95–103.
[55] H.E. Criswell, K.B. Johnson, R.A. Mueller, G.R. Breese, Evidence for involvement of brain dopamine and other mechanisms in the behavioral action of the *N*-methyl-D-aspartic acid antagonist MK-801 in control and 6-hydroxydopamine-lesioned rats, J. Pharmacol. Exp. Ther. 265 (1993) 1001–1010.
[56] E. Davids, K. Zhang, F.I. Tarazi, R.J. Baldessarini, Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning, Psychopharmacology (Berl) 160 (2002) 92–98.
[57] E. Davids, K. Zhang, F.I. Tarazi, R.J. Baldessarini, Animal models of attention-deficit hyperactivity disorder, Brain Res. Brain Res. Rev. 42 (2003) 1–21.
[58] L. Descarries, J.J. Soghomonian, S. Garcia, G. Doucet, J.P. Bruno, Ultrastructural analysis of the serotonin hyperinnervation in adult rat neostriatum following neonatal dopamine denervation with 6-hydroxydopamine, Brain Res. 569 (1992) 1–13.
[59] K.M. Dewar, J.-J. Soghomonian, J.P. Bruno, L. Descarries, T.A. Reader, Elevation of dopamine D2 but not D1 receptors in adult rat neostriatum after neonatal 6-hydroxydopamine denervation, Brain Res. 536 (1990) 287–296.
[60] G.E. Duncan, H.E. Criswell, T.J. McCown, I.A. Paul, R.A. Mueller, G.R. Breese, Behavioral and neurochemical responses to haloperidol and SCH-23390 in rats treated neonatally or as adults with 6-hydroxydopamine, J. Pharmacol. Exp. Ther. 243 (1987) 1027–1034.
[61] G.E. Duncan, G.R. Breese, H.E. Criswell, K.B. Johnson, U.B. Schambra, R.A. Mueller, M.G. Caron, R.T. Fremeau Jr., D1 dopamine receptor binding and mRNA levels are not altered after neonatal 6-hydroxydopamine treatment: evidence against dopamine-mediated induction of D1 dopamine receptors during postnatal development, J. Neurochem. 61 (1993) 1255–1262.
[62] R. Elie, Y. Langlois, S.F. Cooper, G. Gravel, J.-M. Albert, Comparison of SCH-12679 and thioridazine in aggressive mental retardates, Can. J. Psychiatry 25 (1980) 484–491.
[63] M. el Mansari, F. Radja, A. Ferron, T.A. Reader, E. Molina-Holgado, L. Descarries, Hypersensitivity to serotonin and its agonists in serotonin-hyperinnervated neostriatum after neonatal dopamine denervation, Eur. J. Pharmacol. 261 (1994) 171–178.
[64] L. Erinoff, R.C. MacPhail, A. Heller, L.S. Seiden, Age-dependent effects of 6-hydroxydopamine on locomotor activity in the rat, Brain Res. 164 (1979) 195–205.
[65] M. Ernst, A.J. Zametkin, J.A. Matochik, D. Pascualvaca, P.H. Jons, K. Hardy, J.G. Hankerson, D.J. Doudet, R.M. Cohen, Presynaptic dopaminergic deficits in Lesch–Nyhan disease, N. Engl. J. Med. 334 (1996) 1568–1572.
[66] P.A. Frohna, B.S. Neal-Beliveau, J.N. Joyce, Delayed plasticity of the mesolimbic dopamine system following neonatal 6-OHDA lesions, Synapse 25 (1997) 293–305.
[67] R.R. Gainetdinov, W.C. Wetsel, S.R. Jones, E.D. Levin, M. Jaber, M.G. Caron, Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity, Science 283 (1999) 397–401.
[68] S. Garnis-Jones, S. Collins, D. Rosenthal, Treatment of self-mutilation with olanzapine, J. Cutan. Med. Surg. 4 (2000) 161–163.
[69] M.A. Geyer, N.R. Swerdlow, R.S. Mansbach, D.L. Braff, Startle response models of sensorimotor gating and habituation deficits in schizophrenia, Brain Res. Bull. 25 (1990) 485–498.
[70] M.A. Geyer, K. Krebs-Thomson, D.L. Braff, N.R. Swerdlow, Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review, Psychopharmacology (Berl) 156 (2001) 117–154.
[71] S.D. Gleason, H.E. Shannon, Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice, Psychopharmacology (Berl) 129 (1997) 79–84.
[72] L. Gong, R.M. Kostrzewa, Supersensitized oral responses to a serotonin agonist in neonatal 6-OHDA-treated rats, Pharmacol. Biochem. Behav. 41 (1992) 621–623.
[73] L. Gong, R.M. Kostrzewa, R.W. Fuller, K.W. Perry, 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 (1992) 1000–1007.
[74] L. Gong, R.M. Kostrzewa, R. Brus, R.W. Fuller, K.W. Perry, Ontogenetic SKF 38393 treatments sensitize dopamine D1 receptors

in neonatal 6-OHDA-lesioned rats, Brain Res. Dev. Brain Res. 76 (1993) 59–65.
[75] L. Gong, R.M. Kostrzewa, C. Li, Neonatal 6-hydroxydopamine and adult SKF 38393 treatments alter dopamine D1 receptor mRNA levels: absence of other neurochemical associations with the enhanced behavioral responses of lesioned rats, J. Neurochem. 63 (1994) 1282–1290.
[76] R.G. Hammock, S.R. Schroeder, W.R. Levine, The effect of clozapine on self-injurious behavior, J. Autism Dev. Disord. 25 (1995) 611–626.
[77] R. Hammock, W.R. Levine, S.R. Schroeder, Brief report: effects of clozapine on self-injurious behavior of two risperidone nonresponders with mental retardation, J. Autism Dev. Disord. 31 (2001) 109–113.
[78] T.G. Heffner, L.S. Seiden, Possible involvement of serotonergic neurons in the reduction of locomotor hyperactivity caused by amphetamine in neonatal rats depleted of brain dopamine, Brain Res. 244 (1982) 81–90.
[79] G.A. Higgins, M. Enderlin, M. Haman, P.J. Fletcher, The 5-HT2A receptor antagonist M100,907 attenuates motor and 'impulsive-type' behaviours produced by NMDA receptor antagonism, Psychopharmacology (Berl) 170 (2003) 309–319.
[80] A.S. Hollister, G.R. Breese, B.R. Cooper, Comparison of tyrosine hydroxylase and dopamine-beta-hydroxylase inhibition with the effects of various 6-hydroxydopamine treatments on D-amphetamine induced motor activity, Psychopharmacologia 36 (1974) 1–16.
[81] A.S. Hollister, G.R. Breese, C.M. Kuhn, B.R. Cooper, S.M. Schanberg, An inhibitory role for brain serotonin-containing systems in the locomotor effects of D-amphetamine, J. Pharmacol. Exp. Ther. 198 (1976) 12–22.
[82] N.Y. Huang, R.M. Kostrzewa, C. Li, K.W. Perry, R.W. Fuller, Persistent spontaneous oral dyskinesias in haloperidol-withdrawn rats neonatally lesioned with 6-hydroxydopamine: absence of an association with the Bmax for [3H]raclopride binding to neostriatal homogenates, J. Pharmacol. Exp. Ther. 280 (1997) 268–276.
[83] M. Hummel, E.M. Unterwald, D1 dopamine receptor: a putative neurochemical and behavioral link to cocaine action, J. Cell. Physiol. 191 (2002) 17–27.
[84] T.M. Itil, M.J. Stock, A.D. Duffy, A. Esquenazi, B. Saleuty, T.H. Han, Therapeutic trials and EEG investigations with SCH-12,679 in behaviorally disturbed adolescents, Curr. Ther. Res. Clin. Exp. 14 (1972) 136–150.
[85] D.M. Jackson, M. Hashizume, Bromocriptine-induced locomotor stimulation in mice is modulated by dopamine D-1 receptors, J. Neural Transm. 69 (1987) 131–145.
[86] J. Jankovic, J. Caskey, T.C. Stout, I.J. Butler, Lesch–Nyhan syndrome: a study of motor behavior and cerebrospinal fluid neurotransmitters, Ann. Neurol. 23 (1988) 466–469.
[87] D.C. Javitt, S.R. Zukin, Recent advances in the phencyclidine model of schizophrenia, Am. J. Psychiatry 148 (1991) 1301–1308.
[88] J.D. Jentsch, R.H. Roth, The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia, Neuropsychopharmacology 20 (1999) 201–225.
[89] K.B. Johnson, H.E. Criswell, K.F. Jensen, P.E. Simson, R.A. Mueller, G.R. Breese, Comparison of the D1-dopamine agonists SKF-38393 and A-68930 in neonatal 6-hydroxydopamine-lesioned rats: behavioral effects and induction of c-*fos*-like immunoreactivity, J. Pharmacol. Exp. Ther. 262 (1992) 855–865.
[90] R. Karler, L.D. Calder, I.A. Chaudhry, S.A. Turkanis, Blockade of "reverse tolerance" to cocaine and amphetamine by MK-801, Life Sci. 45 (1989) 599–606.
[91] D. Knapp, S.S. Moy, G.R. Breese, Neonatal 6-OHDA Lesions Presistently Activate FosB, COX2, and JunD in the Adult Rat Striatum, ACNP, Abstract, 1999.
[92] R.M. Kostrzewa, D. Neely, Enhanced pilocarpine-induced oral activity responses in neonatal 6-OHDA treated rats, Pharmacol. Biochem. Behav. 45 (1993) 737–740.
[93] R.M. Kostrzewa, R. Brus, K.W. Perry, R.W. Fuller, Age-dependence of a 6-hydroxydopamine lesion on SKF 38393- and *m*-chlorophenylpiperazine-induced oral activity responses of rats, Brain Res. Dev. Brain Res. 76 (1993) 87–93.
[94] R.M. Kostrzewa, R. Brus, M. Rykaczewska, A. Plech, Low-dose quinpirole ontogenically sensitizes to quinpirole-induced yawning in rats, Pharmacol. Biochem. Behav. 44 (1993) 487–489.
[95] R.M. Kostrzewa, L. Gong, R. Brus, Serotonin (5-HT) systems mediate dopamine (DA) receptor supersensitivity, Acta Neurobiol. Exp. (Warsz) 53 (1993) 31–41.
[96] R.M. Kostrzewa, J. Guo, F.P. Kostrzewa, Ontogenetic quinpirole treatment induces vertical jumping activity in rats, Eur. J. Pharmacol. 239 (1993) 183–187.
[97] R.M. Kostrzewa, T.A. Reader, L. Descarries, Serotonin neural adaptations to ontogenetic loss of dopamine neurons in rat brain, J. Neurochem. 70 (1998) 889–898.
[98] R.M. Kostrzewa, R. Brus, K.W. Perry, Interactive modulation by dopamine and serotonin neurons of receptor sensitivity of the alternate neurochemical system, Pol. J. Pharmacol. 51 (1999) 39–47.
[99] G.J. LaHoste, J.M. Swanson, S.B. Wigal, C. Glabe, T. Wigal, N. King, J.L. Kennedy, Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder, Mol. Psychiatry 1 (1996) 121–124.
[100] A.C. Lahti, B. Koffel, D. LaPorte, C.A. Tamminga, Subanesthetic doses of ketamine stimulate psychosis in schizophrenia, Neuropsychopharmacology 13 (1995) 9–19.
[101] M. Lesch, W.L. Nyhan, A familial disorder of uric acid metabolism and central nervous system function, Am. J. Med. 36 (1964) 561–570.
[102] J.A. Lieberman, B.B. Sheitman, B.J. Kinon, Neurochemical sensitization in the pathophysiology of schizophrenia: deficits and dysfunction in neuronal regulation and plasticity, Neuropsychopharmacology 17 (1997) 205–229.
[103] G.S. Linn, S.S. Negi, S.V. Gerum, D.C. Javitt, Reversal of phencyclidine-induced prepulse inhibition deficits by clozapine in monkeys, Psychopharmacology (Berl) 169 (2003) 234–239.
[104] K.G. Lloyd, O. Hornykiewicz, L. Davidson, K. Shannak, I. Farley, M. Goldstein, M. Shibuya, W.N. Kelley, I.H. Fox, Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch–Nyhan syndrome, N. Engl. J. Med. 305 (1981) 1106–1111.
[105] R. Longoni, L. Spina, G. Di Chiara, Permissive role of D-1 receptor stimulation for the expression of D-2 mediated behavioral responses: a quantitive phenomenological study in ras, Life Sci. 41 (1987) 2135–2145.
[106] W. Loscher, D. Honack, The behavioural effects of MK-801 in rats: involvement of dopaminergic, serotonergic and noradrenergic systems, Eur. J. Pharmacol. 215 (1992) 199–208.
[107] J. Luthman, B. Bolioli, T. Tsutsumi, A. Verhofstad, G. Jonsson, Sprouting of striatal serotonin nerve terminals following selective lesions of nigro-striatal dopamine neurons in neonatal rat, Brain Res. Bull. 19 (1987) 269–274.
[108] J. Luthman, A. Fredriksson, T. Lewander, G. Jonsson, T. Archer, Effects of D-amphetamine and methylphenidate on hyperactivity produced by neonatal 6-hydroxydopamine treatment, Psychopharmacology (Berl) 99 (1989) 550–557.
[109] J. Luthman, E. Brodin, E. Sundstrom, B. Wiehager, Studies on brain monoamine and neuropeptide systems after neonatal intracerebroventricular 6-hydroxydopamine treatment, Int. J. Dev. Neurosci. 8 (1990) 549–560.
[110] J. Luthman, E. Lindqvist, D. Young, R. Cowburn, Neonatal dopamine lesion in the rat results in enhanced adenylate cyclase activity without altering dopamine receptor binding or dopamine- and adenosine 3′:5′-monophosphate-regulated phosphoprotein (DARPP-32) immunoreactivity, Exp. Brain Res. 83 (1990) 85–95.

[111] J. Luthman, M. Bassen, A. Fredriksson, T. Archer, Functional changes induced by neonatal cerebral 6-hydroxydopamine treatment: effects of dose levels on behavioral parameters, Behav. Brain Res. 82 (1997) 213–221.
[112] A.K. Malhotra, C.M. Adler, S.D. Kennison, I. Elman, D. Pickar, A. Breier, Clozapine blunts *N*-methyl-D-aspartate antagonist-induced psychosis: a study with ketamine, Biol. Psychiatry 42 (1997) 664–668.
[113] A.K. Malhotra, D.A. Pinals, C.M. Adler, I. Elman, A. Clifton, D. Pickar, A. Breier, Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics, Neuropsychopharmacology 17 (1997) 141–150.
[114] P. Martin, N. Waters, S. Waters, A. Carlsson, M.L. Carlsson, MK-801-induced hyperlocomotion: differential effects of M100907, SDZ PSD 958 and raclopride, Eur. J. Pharmacol. 335 (1997) 107–116.
[115] Y. Masuo, M. Ishidom, M. Morita, S. Oka, Effects of neonatal 6-hydroxydopamine lesion on the gene expression profile in young adult rats, Neurosci. Lett. 335 (2002) 124–128.
[116] S. Maurel-Remy, K. Bervoets, M.J. Millan, Blockade of phencyclidine-induced hyperlocomotion by clozapine and MDL 100,907 in rats reflects antagonism of 5-HT2A receptors, Eur. J. Pharmacol. 280 (1995) R9–R11.
[117] A.C. McCreary, C.A. Marsden, Cocaine-induced behaviour: dopamine D1 receptor antagonism by SCH 23390 prevents expression of conditioned sensitisation following repeated administration of cocaine, Neuropharmacology 32 (1993) 387–391.
[118] M. McDonough, J. Hillery, N. Kennedy, Olanzapine for chronic, stereotypic self-injurious behaviour: a pilot study in seven adults with intellectual disability, J. Intellect. Disabil. Res. 44 (Pt. 6) (2000) 677–684.
[119] E. Meller, F. Bordi, K. Bohmaker, Enhancement by the D1 dopamine agonist SKF 38393 of specific components of stereotypy elicited by the D2 agonists LY 171555 and RU 24213, Life Sci. 42 (1988) 2561–2567.
[120] E. Molina-Holgado, K.M. Dewar, L. Descarries, T.A. Reader, 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 (1994) 713–721.
[121] S.S. Moy, G.R. Breese, Phencyclidine supersensitivity in rats with neonatal dopamine loss, Psychopharmacology (Berl) 161 (2002) 255–262.
[122] S.S. Moy, G.R. Breese, D.A. Eckerman, Altered activity patterns following neonatal 6-hydroxydopamine lesions to dopaminergic neurons: effect of SKF-38393, Brain Res. 645 (1994) 49–60.
[123] S.S. Moy, D.J. Knapp, G.R. Breese, Effect of olanzapine on functional responses from sensitized D1-dopamine receptors in rats with neonatal dopamine loss, Neuropsychopharmacology 25 (2001) 224–233.
[124] S.S. Moy, A. Fernandes, Y. Qian, D.J. Rotella, R.M. Kostrewa, G.R. Breese, Effect of acute and chronic olanzapine treatment on phencyclidine-induced behavioral sensitization in rats with neonatal dopamine loss, Pharmacol. Biochem. Behav. 78 (2004) 47–56.
[125] A. Mrini, J.P. Soucy, F. Lafaille, P. Lemoine, L. Descarries, Quantification of the serotonin hyperinnervation in adult rat neostriatum after neonatal 6-hydroxydopamine lesion of nigral dopamine neurons, Brain Res. 669 (1995) 303–308.
[126] I. Ninan, K.E. Jardemark, R.Y. Wang, Olanzapine and clozapine but not haloperidol reverse subchronic phencyclidine-induced functional hyperactivity of *N*-methyl-D-aspartate receptors in pyramidal cells of the rat medial prefrontal cortex, Neuropharmacology 44 (2003) 462–472.
[127] J.W. Olney, J.W. Newcomer, N.B. Farber, NMDA receptor hypofunction model of schizophrenia, J. Psychiatr. Res. 33 (1999) 523–533.
[128] S.T. Papadeas, B.L. Blake, D.J. Knapp, G.R. Breese, Sustained extracellular signal-regulated kinase 1/2 phosphorylation in neonate 6-hydroxydopamine-lesioned rats after repeated D1-dopamine receptor agonist administration: implications for NMDA receptor involvement, J. Neurosci. 24 (2004) 5863–5876.
[129] A. Parwani, E.J. Duncan, E. Bartlett, S.H. Madonick, T.R. Efferen, R. Rajan, M. Sanfilipo, P.B. Chappell, S. Chakravorty, S. Gonzenbach, G.N. Ko, J.P. Rotrosen, Impaired prepulse inhibition of acoustic startle in schizophrenia, Biol. Psychiatry 47 (2000) 662–669.
[130] M. Poyurovsky, D. Koren, I. Gonopolsky, M. Schneidman, C. Fuchs, A. Weizman, R. Weizman, Effect of the 5-HT2 antagonist mianserin on cognitive dysfunction in chronic schizophrenia patients: an add-on, double-blind placebo-controlled study, Eur. Neuropsychopharmacol. 13 (2003) 123–128.
[131] F. Radja, L. Descarries, K.M. Dewar, T.A. Reader, Serotonin 5-HT1 and 5-HT2 receptors in adult rat brain after neonatal destruction of nigrostriatal dopamine neurons: a quantitative autoradiographic study, Brain Res. 606 (1993) 273–285.
[132] T.A. Reader, K.M. Dewar, Effects of denervation and hyperinnervation on dopamine and serotonin systems in the rat neostriatum: implications for human Parkinson's disease, Neurochem. Int. 34 (1999) 1–21.
[133] J. Scheel-Kruger, G. Magelund, M.C. Olianas, Role of GABA in the striatal output system: globus pallidus, nucleus entopeduncularis, substantia nigra and nucleus subthalamicus, Adv. Biochem. Psychopharmacol. 30 (1981) 165–186.
[134] S.B. Schwarzkopf, T. Mitra, J.P. Bruno, Sensory gating in rats depleted of dopamine as neonates: potential relevance to findings in schizophrenic patients, Biol. Psychiatry 31 (1992) 759–773.
[135] S.B. Schwarzkopf, J.P. Bruno, T. Mitra, J.R. Ison, Effects of haloperidol and SCH 23390 on acoustic startle in animals depleted of dopamine as neonates: implications for neuropsychiatric syndromes, Psychopharmacology (Berl) 123 (1996) 258–266.
[136] J.E. Seegmiller, F.M. Rosenbloom, W.N. Kelley, Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis, Science 155 (1967) 1682–1684.
[137] D.S. Segal, A.J. Mandell, Long-term administration of D-amphetamine: progressive augmentation of motor activity and stereotypy, Pharmacol. Biochem. Behav. 2 (1974) 249–255.
[138] P.E. Setler, H.M. Sarau, C.L. Zirkle, H.L. Saunders, The central effects of a novel dopamine agonist, Eur. J. Pharmacol. 50 (1978) 419–430.
[139] B.A. Shaywitz, J.H. Klopper, R.D. Yager, J.W. Gordon, Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine, Nature 261 (1976) 153–155.
[140] B.A. Shaywitz, R.D. Yager, J.H. Klopper, Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction, Science 191 (1976) 305–308.
[141] B.A. Shaywitz, J.H. Klopper, J.W. Gordon, Methylphenidate in 6-hydroxydopamine-treated developing rat pups. Effects on activity and maze performance, Arch. Neurol. 35 (1978) 463–469.
[142] P.E. Simson, K.B. Johnson, H.A. Jurevics, H.E. Criswell, T.C. Napier, G.E. Duncan, R.A. Mueller, G.R. Breese, Augmented sensitivity of D1-dopamine receptors in lateral but not medial striatum after 6-hydroxydopamine-induced lesions in the neonatal rat, J. Pharmacol. Exp. Ther. 263 (1992) 1454–1463.
[143] S.P. Sivam, D1 dopamine receptor-mediated substance P depletion in the striatonigral neurons of rats subjected to neonatal dopaminergic denervation: implications for self-injurious behavior, Brain Res. 500 (1989) 119–130.
[144] S.P. Sivam, G.R. Breese, J.E. Krause, T.C. Napier, R.A. Mueller, J.S. Hong, Neonatal and adult 6-hydroxydopamine-induced lesions differentially alter tachykinin and enkephalin gene expression, J. Neurochem. 49 (1987) 1623–1633.
[145] S.P. Sivam, J.E. Krause, G.R. Breese, J.S. Hong, Dopamine-dependent postnatal development of enkephalin and tachykinin neurons of rat basal ganglia, J. Neurochem. 56 (1991) 1499–1508.
[146] R.D. Smith, B.R. Cooper, G.R. Breese, Growth and behavioral changes in developing rats treated intracisternally with 6-hydroxy-

dopamine: evidence for involvement of brain dopamine, J. Pharmacol. Exp. Ther. 185 (1973) 609–619.
[147] A.M. Snyder, M.J. Zigmond, R.D. Lund, Sprouting of serotoninergic afferents into striatum after dopamine-depleting lesions in infant rats: a retrograde transport and immunocytochemical study, J. Comp. Neurol. 245 (1986) 274–281.
[148] M. Stachowiak, J.P. Bruno, A.M. Snyder, E.M. Stricker, M.J. Zigmond, Apparent sprouting of striatal serotonergic terminals after dopamine-depleting brain lesions in neonatal rats, Brain Res. 16 (1984) 164–167.
[149] M.S. Starr, B.S. Starr, Behavioural synergism between the dopamine agonists SKF 38393 and LY 171555 in dopamine-depleted mice: antagonism by sulpiride reveals only stimulant postsynaptic D-2 receptors, Pharmacol. Biochem. Behav. 33 (1989) 41–44.
[150] K.E. Stevens, J. Luthman, E. Lindqvist, R.G. Johnson, G.M. Rose, Effects of neonatal dopamine depletion on sensory inhibition in the rat, Pharmacol. Biochem. Behav. 53 (1996) 817–823.
[151] C.J. Stodgell, P.S. Loupe, S.R. Schroeder, R.E. Tessel, Cross-sensitization between footshock stress and apomorphine on self-injurious behavior and neostriatal catecholamines in a rat model of Lesch-Nyhan syndrome, Brain Res. 783 (1998) 10–18.
[152] C.J. Swanson, D.D. Schoepp, The group II metabotropic glutamate receptor agonist (−)-2-oxa-4-aminobicyclo[3.1.0.]hexane-4,6-dicarboxylate (LY379268) and clozapine reverse phencyclidine-induced behaviors in monoamine-depleted rats, J. Pharmacol. Exp. Ther. 303 (2002) 919–927.
[153] A. Snyder-Keller, Development of striatal compartmentalization following pre- or postnatal dopamine depletion, J. Neurosci. 11 (1991) 810–821.
[154] M.S. Szczypka, K. Kwok, M.D. Brot, B.T. Marck, A.M. Matsumoto, B.A. Donahue, R.D. Palmiter, Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice, Neuron 30 (2001) 819–828.
[155] M. Takasuna, T. Iwasaki, Active and passive avoidance learning in rats neonatally treated with intraventricular 6-hydroxydopamine, Behav. Brain Res. 74 (1996) 119–126.
[156] R.F. Thompson, The neurobiology of learning and memory, Science 233 (1986) 941–947.
[157] A.C. Towle, H.E. Criswell, E.H. Maynard, J.M. Lauder, T.H. Joh, R.A. Mueller, G.R. Breese, Serotonergic innervation of the rat caudate following a neonatal 6-hydroxydopamine lesion: an anatomical, biochemical and pharmacological study, Pharmacol. Biochem. Behav. 34 (1989) 367–374.
[158] K. Tsuruta, E.A. Frey, C.W. Grewe, T.E. Cote, R.L. Eskay, J.W. Kebabian, Evidence that LY-141865 specifically stimulates the D-2 dopamine receptor, Nature 292 (1981) 463–465.
[159] U. Ungerstedt, Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system, Acta Physiol. Scand. Suppl. 367 (1971) 95–122.
[160] U. Ungerstedt, Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour, Acta Physiol. Scand. Suppl. 367 (1971) 49–68.
[161] U. Ungerstedt, Use of intracerebral injections of 6-hydroxydopamine as a tool for morphological and functional studies on central catecholamine neurons, in: T. Malmfors, H. Thoenen (Eds.), 6-Hydroxydopamine and Catecholamine Neurons, 1971, pp. 315–332.
[162] J.R. Walters, D.A. Bergstrom, J.H. Carlson, T.N. Chase, A.R. Braun, D1 dopamine receptor activation required for postsynaptic expression of D2 agonist effects, Science 236 (1987) 719–722.
[163] R.Y. Wang, X. Liang, M100907 and clozapine, but not haloperidol or raclopride, prevent phencyclidine-induced blockade of NMDA responses in pyramidal neurons of the rat medial prefrontal cortical slice, Neuropsychopharmacology 19 (1998) 74–85.
[164] F.B. Weihmuller, J.P. Bruno, Drinking behavior and motor function in rat pups depleted of brain dopamine during development, Dev. Psychobiol. 22 (1989) 101–113.
[165] I.Q. Whishaw, D.R. Funk, S.J. Hawryluk, E.D. Karbashewski, Absence of sparing of spatial navigation, skilled forelimb and tongue use and limb posture in the rat after neonatal dopamine depletion, Physiol. Behav. 40 (1987) 247–253.
[166] M.E. Wolf, The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants, Prog. Neurobiol. 54 (1998) 679–720.
[167] A.H. Wong, H.H. Van Tol, The dopamine D4 receptors and mechanisms of antipsychotic atypicality, Prog. Neuro-psychopharmacol. Biol. Psychiatry 27 (2003) 1091–1099.
[168] D.F. Wong, J.C. Harris, S. Naidu, F. Yokoi, S. Marenco, R.F. Dannals, H.T. Ravert, M. Yaster, A. Evans, O. Rousset, R.N. Bryan, A. Gjedde, M.J. Kuhar, G.R. Breese, Dopamine transporters are markedly reduced in Lesch–Nyhan disease in vivo, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 5539–5543.
[169] R.S. Wool, D.A. Weldon, B.A. Shaywitz, G.M. Anderson, D.J. Cohen, M.H. Teicher, Amphetamine reverses learning deficits in 6-hydroxydopamine-treated rat pups, Dev. Psychobiol. 20 (1987) 219–232.
[170] T. Young, G.W. Lawson, C.B. Gacono, Clinical aspects of phencyclidine (PCP), Int. J. Addict. 22 (1987) 1–15.
[171] K. Zhang, F.I. Tarazi, R.J. Baldessarini, Role of dopamine D(4) receptors in motor hyperactivity induced by neonatal 6-hydroxydopamine lesions in rats, Neuropsychopharmacology 25 (2001) 624–632.
[172] K. Zhang, E. Davids, F.I. Tarazi, R.J. Baldessarini, Effects of dopamine D4 receptor-selective antagonists on motor hyperactivity in rats with neonatal 6-hydroxydopamine lesions, Psychopharmacology (Berl) 161 (2002) 100–106.
[173] K. Zhang, F.I. Tarazi, E. Davids, R.J. Baldessarini, Plasticity of dopamine D4 receptors in rat forebrain: temporal association with motor hyperactivity following neonatal 6-hydroxydopamine lesioning, Neuropsychopharmacology 26 (2002) 625–633.