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Effects of Neonatal Dopamine Depletion on Sensory Inhibition in the Rat

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STEVENS, K. E., J. LUTHMAN, E. LINDQVIST, R. G. JOHNSON AND G. M. ROSE. *Effects of neonatal dopamine depletion on sensory inhibition in the rat.* PHARMACOL BIOCHEM BEHAV **53**(4) 817-823, 1996.—Central dopamine systems appear to play an important role in sensory information processing. In particular, the filtering (or gating) of repetitive auditory stimuli is modulated by pharmacological manipulations that affect dopaminergic neurotransmission. The present study further addressed the role of dopamine in auditory gating. Three-day-old male Sprague-Dawley rats, pretreated with desipramine, received intracisternal injections of 6-hydroxydopamine (6-OHDA; 75 μg in 10 μl) or the vehicle. At 4 months of age the rats were implanted for evoked potential recording and auditory gating was assessed using a paired click paradigm. Neonatally administered 6-OHDA did not alter gating in the adult rats. However, unlike for the control group, systemic amphetamine (1.83 mg/kg, IP) failed to disrupt gating in the treated rats. Apomorphine (1.0 mg/kg, SC) disrupted gating in both groups. Neonatal 6-OHDA treatment caused significant reductions in dopamine levels in the striatum, nucleus accumbens, and substantia nigra/ventral tegmental regions. There was an inverse relationship between substantia nigra/ventral tegmental area dopamine levels and auditory gating. Overall, the results suggest that amphetamine-induced auditory gating loss requires presynaptic dopamine release, but that the deficiency occurs through postsynaptic dopamine receptor activation.

Evoked potentials Amphetamine Apomorphine Sensory gating 6-Hydroxydopamine

CENTRAL filtering mechanisms are essential to sensory information processing to avoid input overload (43,44). The adequacy of these central filtering mechanisms can be assessed using a conditioning test paradigm in which two identical stimuli are presented close together (21). When presented with closely paired auditory stimuli, most normal humans show a considerably reduced auditory evoked potential response to the second (or "test") stimulus compared to the first (or "conditioning") stimulus (2,6,23). This attenuation of response is termed auditory gating. In addition to studies in humans, auditory gating has also been demonstrated in laboratory rats (3,4,36,39,40).

Previous studies have suggested an important role for the neurotransmitter dopamine in the modulation of auditory gating in both humans (1,23) and rats (4,36,37). However, this evidence is somewhat indirect, based upon either correlations with plasma levels of dopamine metabolites in humans (1) or the actions of drugs that interact with dopamine systems in rats (4,36,37). A useful and common method for assessing the contribution of a specific neuronal system to a specific behavior or process is to destroy the cells of origin for the neurotransmitter involved. 6-Hydroxydopamine (6-OHDA) is a norepinephrine analogue that induces selective degeneration of catecholaminergic neurons (8,41). By using noradrenergic uptake blockers in conjunction with 6-OHDA administration, selective lesions of dopamine-containing systems can be achieved (11,26,27). This method has been used in both adult and neonatal rats; however, the sequelae vary markedly, depending upon the developmental stage of the animal at the time of the lesion (10,20,22,25,34,35,46). In adults, extensive

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lesions to mesencephalic dopamine neurons renders rats incapable of ingestion and locomotion [(31,42,57); see also (41)]; thus, this approach is impractical for long-term studies. However, following neonatal dopamine lesions through intracisternal (IC) or intracerebroventricular (ICV) administration of 6-OHDA, no obvious disturbance of motor or feeding functions is seen (12,34,45,46). Instead, neonatal lesions produce hyperactivity that persists into adulthood (5,28,34). This hyperactivity appears to require residual function in the remaining dopamine neurons (29), although other transmitter systems may play a role (27). Neonatally dopamine-lesioned rats are also less sensitive to apomorphine-induced (11) or amphetamine-induced (6,19,30) potentiation of locomotor activity than rats lesioned as adults. Interestingly, unlike in the case of adult rats (18), most studies of neonatal dopamine depletion have not been able to detect altered dopamine receptor density, particularly following IC administration of 6-OHDA [(13,30,33); but see (19,32)].

The present study sought to employ neonatal dopamine system depletion to further elucidate the role of dopamine in auditory gating. Auditory evoked potentials were studied in adult rats that had been neonatally treated with 6-OHDA and the results were compared to those obtained in sham-lesioned animals. Additionally, the effects of direct dopaminergic stimulation with apomorphine, or indirect dopaminergic stimulation with *d*-amphetamine, on auditory gating parameters were assessed in both groups of animals. Finally, the rats were sacrificed and tissue levels of catecholamines and metabolites in several brain regions were measured to evaluate the extent and selectivity of the lesions. Correlations between auditory gating parameters and these biochemical data were evaluated.

METHODS

Neonatal 6-OHDA Lesions

On day 3 after birth, male Sprague–Dawley (Alab, Sweden) rats were randomly divided into two groups. The pups were anesthetized by hypothermia; one group received 10 μl IC injections of 6-OHDA [6-OHDA-Br, Sigma Chemical Co.; 75 μg (free base) per 10 μl of 0.9% saline containing 0.2% ascorbic acid] and the other group (sham-lesioned) received the vehicle alone. All animals were pretreated with the noradrenaline uptake blocker, desipramine hydrochloride (DMI, 25 mg/kg, SC, Pertofran, Ciba-Geigy), to protect noradrenergic neurons (26). DMI was administered 30 min prior to the IC injections. Following surgery, the pups were warmed and returned to the mother. Subsequent experimental manipulations were begun approximately 120 days later.

Electrode Implantation Surgery

The adult rats (400–500 g, approximately 4 months old) were implanted for auditory evoked potential recording in the manner previously described (36). Briefly, under sodium pentobarbital anesthesia (50 mg/kg, IP) with methoxyflurane as auxiliary, the rats were stereotaxically implanted with a skull-screw recording electrode placed on dura at "vertex" (−4.0 mm from bregma, on midline). Reference electrodes were placed on dura, 2.0 mm anterior to bregma and 1.0 mm to either side of midline. The electrode leads were gathered into a headpiece that was cemented to the skull using anchoring screws and acrylic dental cement. The rats were allowed to recover for a minimum of 1 week prior to evoked potential recording.

Electrophysiological Recording

The recording chamber, apparatus, and methods have been described previously (36). Briefly, animals were handled for 10–15 min prior to placement in the recording chamber. Following connection to the recording cable and placement in the chamber, the animal was allowed to acclimate for an additional 10 min. Recording sessions consisted of computer-controlled presentations of pairs of click stimuli [1-ms duration, 87 dB (SPL); 0.5-s interval between clicks] that were given at 15-s intervals. Only evoked potentials recorded when the animal was still and alert were accepted for storage and analysis by the computer. Normally, 20–30 still-alert trials were accumulated in a recording session.

Following a recording session, accumulated trials were computer averaged and the latencies from stimulus onset to peak of the evoked waveform for the conditioning (first click) and test (second click) stimuli were calculated (CLAT and TLAT, respectively). The amplitude of the conditioning and test waveforms (CAMP and TAMP, respectively) were calculated from baseline (averaged EEG activity for the 100 ms prior to stimulus onset) to the peak of the negative-going waveform. The TC ratio, a measure of auditory gating, was determined by dividing the test amplitude (TAMP) by the conditioning amplitude (CAMP). All animals experienced 10 recording sessions (baseline sessions, one session per day) prior to drug administration.

On drug treatment days, the animal was given either 1.0 mg/kg apomorphine, SC, a dose that has been shown to increase locomotor activity (9), or 1.83 mg/kg *d*-amphetamine, IP, a dose that is known to effect auditory gating (36). Both drugs were obtained from Sigma Chemical Co (St. Louis, MO) and were prepared in a physiological saline vehicle. All animals received both drugs, with order of presentation randomized. Recording sessions began 20 min following injection. Trials were collected and averaged for the 20–45-min and 45–65-min postinjection intervals.

Monoamine Assay

On completion of the drug experiments, animals were anesthetized with methoxyflurane and sacrificed by decapitation. The brains were rapidly removed and chilled in saline (4°C) before regional dissection. The brains were sliced in roughly 1-mm-thick sections; bilateral 2-mm-diameter punches were then taken from the following regions based on previous studies by Archer and colleagues (5): lateral prefrontal cortex, rostral dorsal striatum, caudal striatum, nucleus accumbens, hippocampus, and substantia nigra/ventral tegmental area (see Fig. 1). The brain samples were immediately frozen in dry ice snow and stored at −70°C for later analysis. Samples were processed using HPLC, with electrochemical detection, as previously described (28). Briefly, all tissues were homogenized by sonication in 5 volumes (5 μl/mg tissue) of 0.1 M perchloric acid followed by centrifugation. The endogenous tissue levels of norepinephrine, dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) were determined in the supernatant. All neurotransmitter and metabolite values are expressed as ng/g wet tissue.

Data Analysis

Data were analyzed by two-way analysis of variance (ANOVA) with Tukey–Kramer *a posteriori* analysis. Indepen-

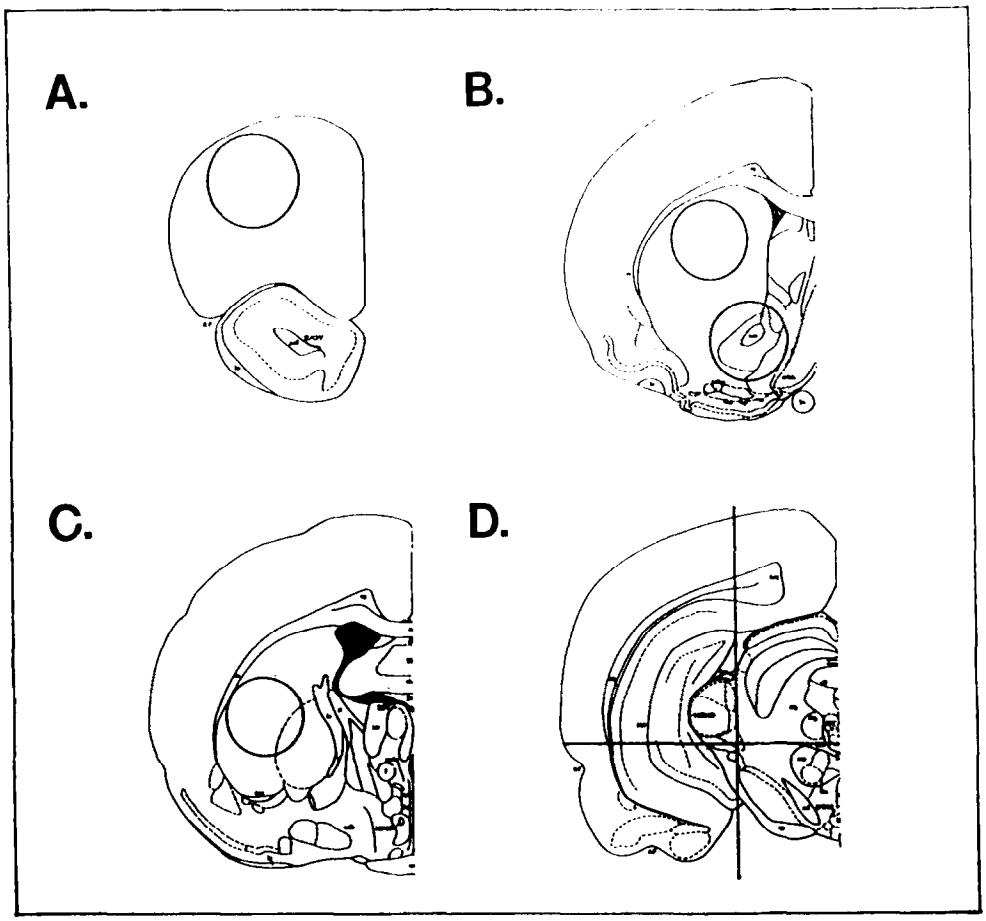

FIG. 1. Diagram of brain areas sampled for HPLC analysis for catecholamines. The brain was sliced into approximately 1-mm-thick sections. Punches 2 mm in diameter were obtained from the areas shown: (A) prefrontal cortex; (B) rostral dorsal striatum (upper), and nucleus accumbens (lower); (C) caudal striatum. Two additional areas, shown in (D), were dissected for analysis: the substantia nigra/ventral tegmental area (ventral medial quadrant of D) and the hippocampus.

dent *t*-tests were used to assess differences in tissue monoamine levels between lesioned and control groups and Pearson's *r* correlation was used to assess potential relationships between measured parameters. An alpha value of $p < 0.05$ was adopted throughout the experiment.

RESULTS

Baseline Recordings

The primary auditory potential recorded from the vertex electrode was a negative-going wave with a latency to peak of approximately 30 ms after stimulus onset (N30; see Fig. 2 for averaged examples). There was a change in the overall ability to gate the response to paired auditory stimuli over recording sessions, with later sessions showing better sensory gating. This pattern of improved gating over the first 10 recording sessions has previously been observed (36,37,39,40), and is likely due to acclimation of the animal to handling and the novel environment of the recording chamber. All animals displayed stable response patterns by the eighth recording session. For analysis purposes, data from the 10th recording session were used as the baseline, unmedicated comparator. Comparisons of sham and lesion groups on the 10th baseline session showed no differences on any auditory gating parameter measured (Table 1).

Effects of Apomorphine or Amphetamine Administration

Apomorphine (1.0 mg/kg, SC) produced a significant increase in TC ratio in both sham and lesioned animals at 20–45 min postinjection, $F(1, 187) = 10.81$, $p = 0.001$. This increase was of equivalent magnitude for both groups, $F(1, 187) = 2.48$, $p = 0.12$. The increase in TC ratio was primarily the result of a large decrease in CAMP, $F(1, 187) = 49.24$, $p < 0.001$, because a small decrease in TAMP was also observed, $F(1, 187) = 9.39$, $p = 0.003$. A significant increase in both CLAT, $F(1, 27) = 36.61$, $p < 0.001$, and TLAT, $F(1, 27) = 24.82$, $p < 0.001$, was found in both sham and lesioned animals in this time frame. Examples of the effects of apomorphine on auditory evoked potentials are shown in Fig. 2. The data are summarized in Table 1.

Amphetamine (1.83 mg/kg, IP) had a differential effect on auditory gating in the sham and lesioned rats, $F(1, 187) = 3.63$, $p = 0.05$. The TC ratio was increased only in sham animals ($p < 0.05$, *a posteriori* analysis), the consequence of a significant decrease in CAMP [$F(1, 187) = 4.73$, $p = 0.03$;

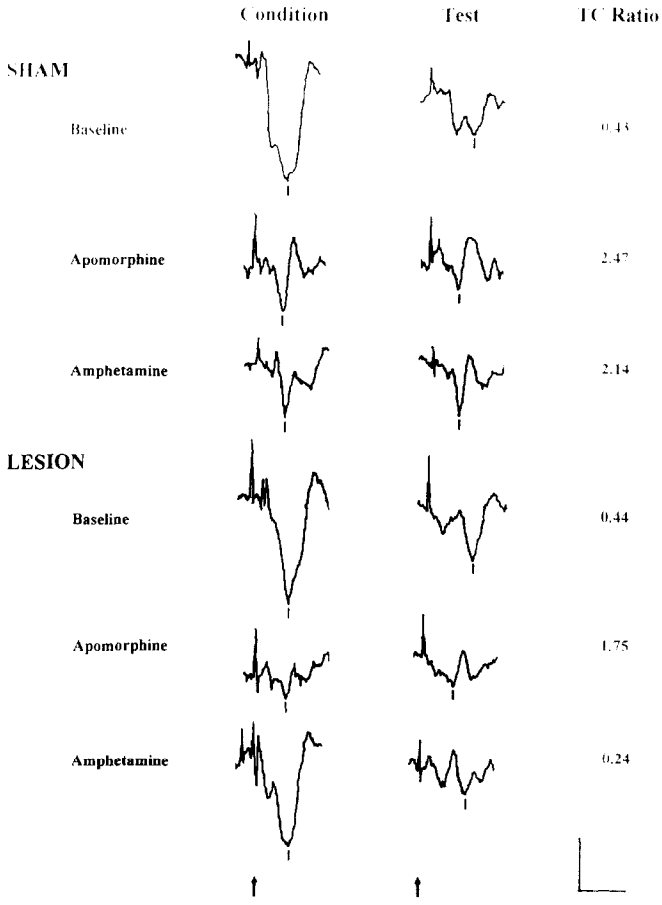

FIG. 2. Representative evoked potentials from a sham and a lesion rat in the unmedicated state (baseline), 20–45 min after apomorphine (1 mg/kg, SC), or 45–64 min after *d*-amphetamine (1.83 mg/kg, IP). TC ratio is calculated as test amplitude/condition amplitude. Baseline recordings of sham and lesion groups did not differ and both groups showed loss of gating following apomorphine administration. However, only the sham group had disrupted gating following amphetamine injection. Ticks mark the peak of the waveform; arrows indicate stimulus onset. Calibration: 50 μV, 50 ms.

$p < 0.05$, *a posteriori* analysis]. Unlike apomorphine, amphetamine produced no change in TAMP, $F(1, 187) = 0.01$, $p = 0.91$. There was no significant alteration in either latency measurement for either group after amphetamine administration. These data are summarized in Table 1; examples of evoked potentials are shown in Fig. 2.

Biochemistry and Correlations With Auditory Gating

Rats that had received neonatal 6-OHDA lesions showed an average 85% depletion of dopamine in the rostro-dorsal striatum (Table 2); however, across individual rats the values ranged from −53% to −98%. In the caudal striatum, an average dopamine depletion of 89% was observed (range: −73% to −95%), whereas in the nucleus accumbens there was an average depletion of 72% (range: −39% to −93%). The area of the substantia nigra/ventral tegmental area had an average dopamine depletion of 64% (range: −27% to −85%). The lateral prefrontal cortex and the hippocampus did not show a lesion-induced reduction in dopamine levels. Independent *t*-tests comparing lesioned to sham animals in the six brain regions tested showed significant reductions of dopamine, and its metabolites DOPAC and HVA, in all brain regions except the cortex and the hippocampus. In contrast, 5-HT levels were not altered in any brain region except the striatum, where they were significantly increased (rostro-dorsal striatum: mean +59%, range 0 to +106%; caudal striatum: mean +55%, range −17% to +101%). Significant changes in levels of the 5-HT metabolite 5-HIAA were not seen in any brain region. There were also no significant changes observed in norepinephrine in any brain region.

Auditory gating parameters were correlated with tissue levels of dopamine, norepinephrine, serotonin, and their metabolites in the various brain regions. Only in the region of the dopaminergic cell bodies, the substantia nigra/ventral tegmental area, were significant negative correlations between dopamine, and its metabolite DOPAC, with the TC ratio found for the lesioned animals ($r = -0.73$, $p = 0.04$ and $r = -0.75$, $p = 0.03$, respectively). No significant correlations were observed in sham animals. There were no significant correlations between levels of norepinephrine, 5-HT, or 5-HIAA with auditory gating for any brain area examined.

DISCUSSION

The present study sought to determine the effect of neonatal dopamine depletion, achieved through intracisternal 6-OHDA administration, upon central sensory filtering processes in the adult rat and to ascertain if such depletion would alter the response to dopaminergic drugs. The adequacy of these central sensory filtering processes was assessed through a "gating" paradigm in which the responses to closely paired auditory stimuli were determined and the degree of filtering or reduction in the response to the second stimulus was calculated. There were two main findings from this study: 1) the neonatal 6-OHDA treatment did not, by itself, affect auditory gating; and 2) apomorphine, but not *d*-amphetamine, pro-

TABLE 1

GATING PARAMETERS FOR 6-HYDROXYDOPAMINE-LESIONED AND SHAM-LESIONED ANIMALS UNDER BASELINE AND DRUG-TREATED CONDITIONS

	Baseline	Apomorphine*	Amphetamine†
Sham			
CAMP	125.6 ± 9.3	60.3 ± 19.6‡	60.1 ± 11.5‡
TAMP	55.4 ± 5.8	38.1 ± 6.9‡	34.7 ± 4.9‡
TC ratio	0.48 ± 0.09	1.18 ± 0.35‡	0.87 ± 0.14‡
CLAT	32.8 ± 1.2	40.1 ± 1.3‡	37.6 ± 1.9
TLAT	32.8 ± 1.4	40.6 ± 2.2‡	36.7 ± 1.3
Lesion			
CAMP	125.4 ± 10.9	47.5 ± 7.8‡	89.1 ± 15.6
TAMP	47.3 ± 5.6	36.2 ± 12.0‡	37.7 ± 3.9
TC ratio	0.39 ± 0.05	1.06 ± 0.38‡	0.53 ± 0.16
CLAT	35.5 ± 1.2	43.1 ± 1.3‡	36.0 ± 0.9
TLAT	35.0 ± 0.9	41.0 ± 1.0‡	36.4 ± 0.8

All data are expressed as mean ± SEM. CAMP and TAMP are expressed in μV, CLAT and TLAT in ms; TC ratio = TAMP/CAMP.

$N = 8$ in all cases.

*20–45 min after injection of 1 mg/kg, SC.

†45–65 min after injection of 1.83 mg/kg, IP.

‡$p < 0.05$ compared to baseline.

TABLE 2

CATECHOLAMINE AND METABOLITE LEVELS MEASURED IN SHAM AND LESIONED RATS IN VARIOUS BRAIN REGIONS

	DA	DOPAC	HVA	5-HT	5-HIAA	NE
Prefrontal cortex						
S	35 ± 4	ND	26 ± 2	508 ± 36	162 ± 19	396 ± 30
L	30 ± 4	ND	ND	522 ± 16	156 ± 18	448 ± 18
Rostro-dorsal striatum						
S	14846 ± 1080	1940 ± 219	745 ± 42	371 ± 39	546 ± 107	ND
L	2298 ± 864*	449 ± 148*	214 ± 57*	590 ± 53†	613 ± 43	ND
Nucleus accumbens						
S	7847 ± 711	1604 ± 138	628 ± 58	715 ± 74	545 ± 58	430 ± 122
L	2224 ± 486*	520 ± 112*	218 ± 31*	856 ± 84	556 ± 34	252 ± 39
Caudal striatum						
S	7583 ± 1018	1318 ± 189	621 ± 99	670 ± 78	674 ± 125	ND
L	866 ± 215*	156 ± 36*	118 ± 23*	1041 ± 101†	786 ± 61	ND
Hippocampus						
S	29 ± 2	ND	ND	419 ± 28	446 ± 48	367 ± 16
L	25 ± 2	ND	ND	440 ± 27	397 ± 9	342 ± 26
Substantia nigra/ventral tegmental area						
S	377 ± 38	72 ± 11	77 ± 9	1123 ± 66	536 ± 63	603 ± 62
L	137 ± 25*	24 ± 6†	47 ± 3†	941 ± 62	521 ± 46	577 ± 67

Data are measured in ng/g wet tissue and expressed as mean ± SEM. S = sham-lesioned, L = 6-hydroxydopamine-lesioned. $N = 8$ for both groups. ND = not detected. *$p < 0.001$, †$p < 0.01$ compared to sham lesion group.

duced a loss of auditory gating in the neonatally 6-OHDA-treated rats.

Analysis of baseline data showed that there was no overall difference between sham and neonatal 6-OHDA-lesioned groups with respect to unmedicated auditory gating. However, in the lesioned animals, significant correlations were observed between gating and both dopamine and DOPAC levels in the substantia nigra and ventral tegmental area. That this correlation was not seen for sham animals is likely to be due to the lack of variability for the dopamine levels that were observed in this group. It therefore appears that an important site for the regulation of auditory gating may be the mesencephalic dopamine neurons.

The administration of the direct dopaminergic agonist, apomorphine, produced a loss of gating in both sham and lesioned animals. It has been shown that neonatal 6-OHDA lesions do not generally result in an upregulation of the numbers of either dopamine receptor subtypes in adulthood (13,30). One group has reported an upregulation of D_2 binding and a downregulation of D_1 binding after ICV administration of 6-OHDA (19,32). However, we have previously shown that the 6-OHDA treatment employed in the present study does not alter D_1 or D_2 receptors (30). In another experiment, neonatal 6-OHDA administration was shown to result in a D_1 receptor supersensitivity with regards to adenylyl cyclase activity (16,30). The lack of difference in the effect of apomorphine on auditory gating between neonatally 6-OHDA-treated animals and sham animals is consistent with no change in dopamine receptor populations, although the possibility of altered sequelae following receptor activation has not been ruled out.

In another auditory gating paradigm, Schwarzkopf et al. (33) found that apomorphine given to neonatally dopamine-lesioned rats caused an additional decrease in prepulse inhibition (PPI) of acoustic startle compared to sham-treated animals. This finding is somewhat in contrast to the present results. However, others have shown that apomorphine only disrupts PPI when relatively weak prepulses are used, and that this occurs because detection of the prepulse is reduced, instead of directly interfering with the mechanisms that mediate PPI itself (17,18). The apparent inconsistency between the present study and that of Schwarzkopf et al. (33) is therefore likely be due to differences in the paradigm used to assess sensory gating.

In contrast to the apomorphine results, amphetamine produced a differential effect on auditory gating between sham and lesioned rats. There was a significant loss of gating in sham animals, in agreement with several other studies demonstrating a loss of auditory gating in both anesthetized (7) and awake animals (3,4,36) following amphetamine administration. By contrast, lesioned animals showed no change in auditory gating following an injection of amphetamine. This may be attributed to the loss of the presynaptic dopaminergic terminals induced by the 6-OHDA and the subsequent disappearance of the capacity of amphetamine to induce an increase in extracellular dopamine (15,24). Because amphetamine works as an indirect agonist by releasing dopamine and blocking presynaptic reuptake (14), the presence of intact presynaptic dopaminergic terminals should be necessary to produce an effect. It is also known that amphetamine administration results in elevated levels of extracellular norepinephrine and serotonin, which can also affect auditory gating (3,36,38–40). An important result of the present study is the indication that these neurotransmitters cannot influence auditory gating in the absence of an intact dopamine system.

In summary, neonatal dopamine depletion through IC administration of 6-OHDA does not affect the ability of the adult rat to gate responses to paired auditory stimuli. However, activation of dopaminergic receptors produced a loss of auditory gating, primarily through a decrease in the amplitude of the response to the first stimulus (CAMP). Thus, the loss

of dopaminergic input in neonatal 6-OHDA-lesioned rats impairs the ability of indirect, but not direct, dopaminergic agonists to modulate gating. These data provide additional support for a central role for dopaminergic pathways in the regulation of auditory gating.

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