Pharmacology Biochemistry & Behavior, Vol. 13, pp. 685–690. Printed in the U.S.A.

Chronic Administration of Haloperidol During Development: Later Psychopharmacological Responses to Apomorphine and Arecoline[1]

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Received 14 June 1980

SHALABY, I. A. AND L. P. SPEAR. *Chronic administration of haloperidol during development: Later psychopharmacological responses to apomorphine and arecoline.* PHARM. BIOCHEM. BEHAV. 13(5) 685–690, 1980.—Offspring of pregnant rats injected with 0.25 mg/kg of haloperidol or saline throughout gestation and until weaning were psychopharmacologically tested for their responsiveness to arecoline and apomorphine. On postnatal day 50, offspring of such chronic treatments were tested in the open field after administration of 0, 0.05, 0.1, 1.0 or 3.0 mg/kg apomorphine, a dopamine agonist. The two chronic treatment groups did not differ in response to high doses of apomorphine which induced stereotyped sniffing and a depression of matrix crossing behavior. However, while control offspring exhibited a low dose (0.05 mg/kg apomorphine) suppression of matrix crossings and rearing behavior, haloperidol treated offspring did not, which may indicate a functional hyposensitivity of dopaminergic autoreceptors in these treated animals. When tested at postnatal day 65 for their cataleptic responses to the cholinergic agonist arecoline, haloperidol treated offspring were more cataleptic to 2 and 5 mg/kg arecoline than control offspring. This suggests that chronic dopamine receptor blockade during development may have long-term indirect effects on the sensitivity of the cholinergic system.

Apomorphine Chronic haloperidol Developmental psychopharmacology Arecoline
Dopaminergic-cholinergic interactions Behavioral teratology

AFTER chronic treatment with dopamine receptor blockers, adult animals in the withdrawal phase exhibit apparent dopaminergic supersensitivity. The animals are spontaneously hyperactive, and are more sensitive to the locomotor stimulating effects of dopamine agonists such as apomorphine and amphetamine [11,24] and less sensitive to the cataleptic actions of dopamine antagonist neuroleptics such as haloperidol [3]. These psychopharmacological indications of dopamine receptor supersensitivity are biochemically characterized, in both striatal and mesolimbic dopamine-rich areas, by an increase in dopamine receptor binding due to an increase in the number of receptors without change in affinity [17]. In view of the pervasiveness of compensatory processes within the nervous system, it is not surprising that other neurotransmitter systems also have been shown to be indirectly affected by such chronic neuroleptic treatment. Repeated treatment with haloperidol has been shown to induce a psychopharmacological supersensitivity to alpha-adrenergic stimulants [13] and hyposensitivity towards cholinergic stimulation [7,10].

Chronic administration during ontogeny of drugs that block dopamine-receptors has been shown to affect later development. For example, rats treated with neuroleptics during development show deficits in active avoidance [1] and rotorod performance [25], and have been reported to be hyperactive in the open field when tested four weeks postnatally, but hypoactive when tested at eight or 12 weeks postnatally [2]. Neurochemically, this treatment results in decreases in tryptophan and tyrosine hydroxylation, and decreases in dopamine synthesis and utilization (e.g., [15]). Psychopharmacologically, intraperitoneal administration of high doses of apomorphine prenatally has been shown to decrease the later responsiveness to the behavioral effects of apomorphine as well as decrease the number of striatal dopamine receptors, while such treatments postnatally appear to enhance apomorphine psychopharmacological responsiveness and increase the number of striatal dopamine receptors [22].

In a previous report [23] we have examined in detail the effects of low doses of haloperidol administration from the

[1]This research was supported in part by Grants 1 R03 MH 29834-01 MSM and 1 R01 MN 33215-01 from the National Institute of Mental Health, and Grant 0005-02-040-76 0 from the Research Foundation of the State University of New York.

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first day of gestation to the 21st postnatal day on later offspring behavior. Haloperidol treated offspring tested shortly after weaning (3–4 weeks of age) or as young adults (7–8 weeks of age) were slightly hyperactive in the open field under non-drug conditions, and exhibited a decreased responsiveness to the locomotor stimulating effects of amphetamine, and an increased responsiveness to the cataleptic effects of haloperidol. From the above study, it seems that chronic haloperidol treatment throughout the prenatal and early postnatal stages may result in a functional decrease in the dopamine systems' sensitivity to stimulation that is seen both shortly after weaning and in adulthood.

The present study was designed to further elucidate the psychopharmacological effects of long term neuroleptic administration on development. Young adult offspring (7–9 weeks of age) treated with haloperidol from the beginning of gestation until weaning were assessed for psychopharmacological responsiveness to low and high doses of the dopamine agonist, apomorphine, as well as to a cholinergic agonist, arecoline. The use of low doses of apomorphine was designed to psychopharmacologically assess the functional status of dopamine autoreceptors [6], while the large doses were designed to assess sensitivity of postsynaptic dopamine receptors [9]. Much interest has lately been directed toward autoreceptors and their functional significance in modulating dopamine synthesis and release. No previous studies have assessed the pharmacological status of autoreceptors after chronic drug treatment during development. In this study, the psychopharmacological responsivity to cholinergic stimulation was also assessed by examining the responsiveness to the cataleptic effects of the cholinergic agonist, arecoline. Since dopaminergic nerve endings appear to terminate in part on cholinergic interneurons in striatum and mesolimbic terminal regions (e.g., [4]), the functional status of cholinergic neurons might well be altered after chronic neuroleptic treatment during development. While it is known that chronic neuroleptic treatment in adult animals produces psychopharmacological hyposensitivity to cholinergic stimulation [7,10], there is a lack of information about the function status of cholinergic systems after chronic neuroleptic treatment during ontogeny.

METHOD

Subjects and Chronic Drug Administration

Male and female Sprague-Dawley albino rats (Blue Spruce Farms) weighing 240–350 g, were used as breeding stock for the subjects used in this study. Chronic drug injections began on Day 1 of gestation, defined as the day on which a copulatory plug was seen or on which sperm were detected in the vagina. Animals were maintained on a 12:12 hr light/dark cycle (lights on at 0700 hr). Food (Purina Rat Chow) and water were continuously available.

The chronic injection procedure consisted of injecting the maternal females subcutaneously in the nape of the neck twice a day (1000 hrs and 2200 hrs) with 0.25 mg/kg/cc haloperidol diluted with distilled water from a 2 mg/cc solution of Haldol Concentrate (McNeil Labs., Inc.) or 0.9% saline control solution. A red light was used to illuminate the room for injections during the dark cycle. Females were weighed once each day, prior to the morning injection. All injections began on the first day of gestation and continued post-partum until the offspring were weaned on postnatal day (P) 21. Injections were not given on those days when a mother gave birth if a mother was in the process of giving birth at the time of the injection. All females (both haloperidol and control) gave birth on the 21–22nd day of gestation.

Litters were culled to ten within twenty-four hours of birth. Eight to ten pups from each of 10 litters (5 haloperidol and 5 control) were used in this study. At weaning, offspring were singly housed.

Behavioral Testing

All drug solutions for the psychopharmacological testing were coded so that the test observers were uninformed as to the contents of a given test solution. Between 7 and 10 animals from each chronic condition were tested under each of the drug conditions. Both male and female offspring from each litter were randomly placed into each of the experimental testing groups with no more than two animals per litter in any experimental group.

Apomorphine. Offspring were tested on P47-50 in an open field apparatus. The open field consisted of a high walled rectangular grey wooden box (70.3×55.8×44.7 cm) with a grey opaque Plexiglas floor that was marked off into 12 matrix squares each of which measured 18.8×16.5 cm. The apparatus was illuminated with two 60 watt white light bulbs in 10 in. reflectors which were located approximately 1 m. above the apparatus floor. Animals were individually handled for five minutes per day on each of the four days proceeding the open field testing (P43-P46). The first three days of open field testing (P47-P49) were used for adapting the animals to the apparatus. On these days, animals were placed individually into the open field for a 10 min period. On the fourth day of testing (P50), animals were given a subcutaneous injection (into the nape of the neck) of 0.05, 0.1, 1.0, 3.0 mg/kg/cc apomorphine hydrochloride (Merck Co.) dissolved in a 0.9% saline solution containing 0.1% ascorbate, or the vehicle alone (0 mg/kg/cc). Twenty minutes post-injection, each animal was given a 10 minute open field test. During the open field test, observers recorded the number of matrix crossings, grooming and scratching bouts, number of rears (supported and unsupported) and total time spent in stereotyped sniffing. Stereotyped sniffing was defined as sniffing with the animal's snouts directed towards the floor of the apparatus.

Arecoline. On P65, the same offspring were tested for arecoline induced catalepsy. Animals under each of the previous acute testing groups were randomly placed into the arecoline treatment groups with the constraint that an equal representation of each of the previous testing groups be placed into each of the arecoline testing groups. Animals were intraperitoneally injected with either saline (0 mg/kg/cc), 2, 5, or 10 mg/kg/cc arecoline hydrochloride (Sigma) 1 min before the catalepsy test. Thereafter, animals were tested for cataleptic behavior every minute for a total of 10 observations. The catalepsy test consisted of placing the animal's forelimbs securely over a 23.4×0.5 cm wooden dowel supported at each end by plywood boards connected to a plywood base which firmly held the dowel parallel to the wooden base and 16.3 cm above it. The animal's body was held in this position over the dowel for about 2 sec prior to removing this manual support. The time it took the animal to change this abnormal position was recorded over an observation period for each test of 30 sec. Animals were considered cataleptic if they remained with their forearms spread over the bar for 10 sec or more. Animals that fell or crawled off of the bar within this 10 sec period were considered to be non-catalpetic.

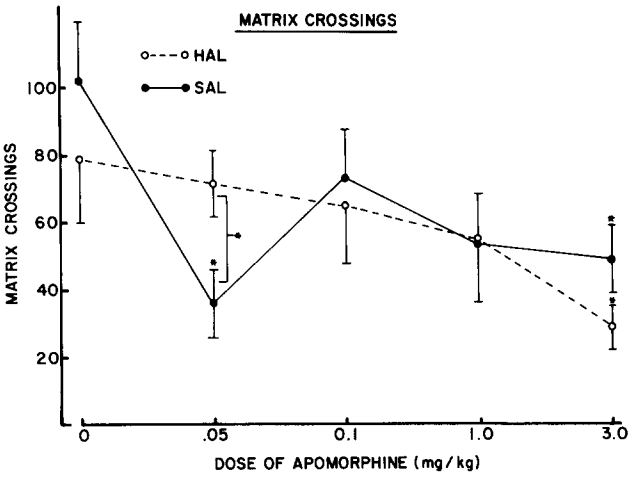

FIG. 1. Effect of apomorphine on matrix crossings (mean±SEM) in offspring of haloperidol treated (HAL) and saline treated (SAL) litters. *$p \leq 0.05$.

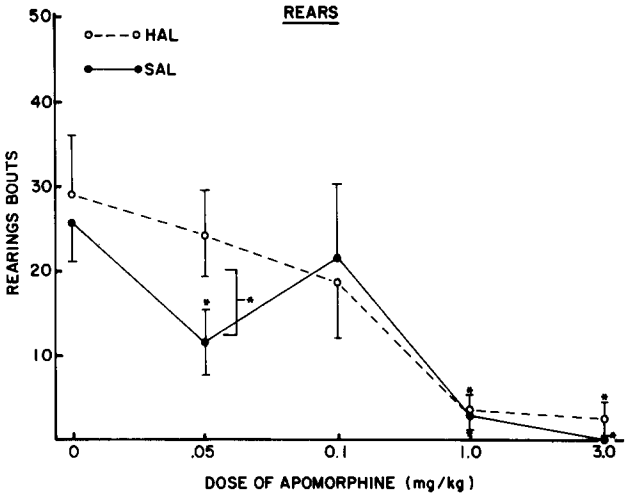

FIG. 2. Effect of apomorphine on rearing behavior (mean±SEM) in offspring of haloperidol treated (HAL) and saline treated (SAL) litters. *$p \leq 0.05$.

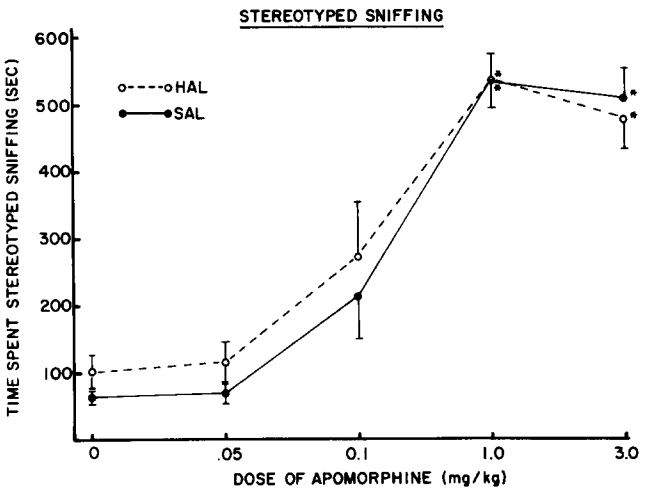

FIG. 3. Effect of apomorphine on stereotyped sniffing (mean±SEM) in offspring of apomorphine treated (HAL) and saline treated (SAL) litters. *$p \leq 0.05$.

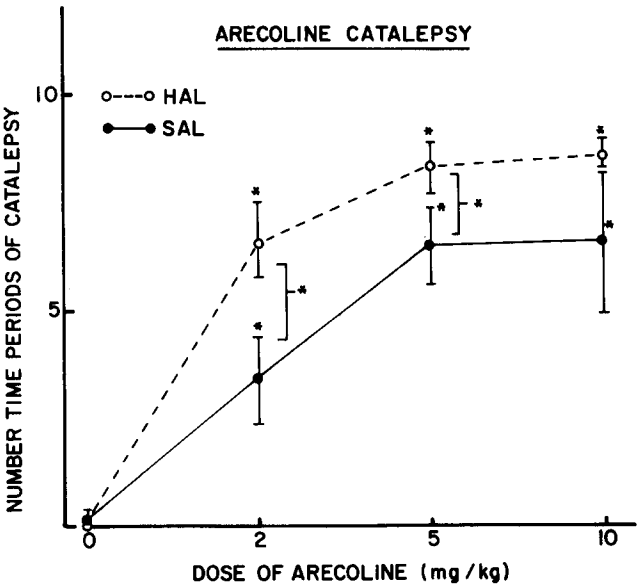

FIG. 4. Effect of arecoline on the number of time periods of catalepsy (mean±SEM) in offspring of haloperidol treated (HAL) and saline treated (SAL) litters. *$p \leq 0.05$.

RESULTS

Body Weights

At postnatal day 50 and 65 offspring of haloperidol treated mothers were significantly heavier than control offspring (for example, at P50: male haloperidol—233.2±3.19, male control—215.3±5.21, $t(42)=2.864$, $p<0.01$; female haloperidol-172.8±3.25, female control—158.9±3.09, $t(41)=3.039$, $p \leq 0.01$). These results are in agreement with Ahlenius and associates [1] who also reported an increased body weight in young adult animals after neuroleptic treatment during the early postnatal period. This alteration in body weight is not seen at birth or at weaning [23], and appears to develop between 4 and 8 weeks postnatally [1].

Psychopharmacological Testing

Preliminary analyses indicated no significant litter effects in any of the behavioral data.

Mann-Whitney *U*-tests were used for statistical comparisons between the offspring of the two chronic treatments in the apomorphine and arecoline testing. These tests were also used to determine, within each of the treatment conditions, differences among animals given the control solution and the various doses of arecoline or apomorphine. Differences were determined to be significant if they attained the 95% confidence interval ($p \leq 0.05$).

There was no differential responsiveness between offspring of haloperidol treated mothers and controls in any behavior on the three adaptation open-field test days.

Matrix crossings of both haloperidol treated and control offspring were significantly decreased by the high dose (3 mg/kg) of apomorphine (see Fig. 1). However, 0.05 mg/kg apomorphine decreased matrix crossings only in control off-

spring. At this dose the control animals exhibited significantly fewer matrix crossings than the haloperidol treated animals.

Rearing Behavior was similarly affected by apomorphine (see Fig. 2). Offspring of both haloperidol and saline treated mothers showed significantly less rearing behavior in response to the two high doses of apomorphine (1.0 and 3.0 mg/kg). However, only the control offspring showed a significant depression of rearing behavior in response to the low dose of apomorphine (0.05 mg/kg). When the two chronic conditions were compared at this low dose, the control offspring exhibited significantly less rearing behavior than the haloperidol treated animals.

Stereotyped Sniffing was significantly increased in offspring of both haloperidol and saline treated mothers in response to the high doses of apomorphine (1.0 and 3.0 mg/kg) (see Fig. 3). There was no differential responsiveness between the chronic groups in terms of stereotyped sniffing.

Grooming and Scratching was not affected by any apomorphine dose.

Arecoline Catalepsy results are displayed in Fig. 4. All doses of arecoline significantly increased the number of cataleptic responses in offspring of both chronic conditions. However, haloperidol treated offspring were more cataleptic than the control offspring in response to 2 and 5 mg/kg arecoline.

DISCUSSION

In the present study, the behavioral effects of low doses of apomorphine were markedly attenuated among chronic haloperidol treated offspring. Low doses of apomorphine have been shown to induce behavioral sedation in adults, presumably due to preferential stimulation of dopamine autoreceptors [6]. Dopamine autoreceptors have been hypothesized to be located on dopaminergic cell bodies and presynaptic terminals, and are thought to exert an inhibitory feedback influence on dopamine synthesis and release [18]. The attenuated responsiveness of chronic haloperidol treated offspring to low doses of apomorphine therefore may indicate a hyposensitivity or deficiency in the number of these regulatory autoreceptors. Indeed, Engel and Lundborg [8] reported a decrease in dopamine turnover following early penfluridol pretreatment which they suggested may be partly due to altered feedback mechanisms. Autoreceptor sensitivity has also been shown to be affected in adult animals treated with neuroleptics, but in the opposite direction. Nowycky and Roth [19] have observed that dopamine autoreceptors were biochemically and electrophysiologically supersensitive to stimulation following chronic pretreatment of adult rats with fluphenazine.

In contrast to the marked difference in responsiveness to low doses of apomorphine, no differences were observed between the haloperidol pretreated offspring and their controls in responsiveness to higher doses of apomorphine. Since these higher doses of apomorphine presumably stimulate dopamine postsynaptic receptors as well as autoreceptors, there is no evidence of any difference in dopamine postsynaptic sensitivity between the treated groups. It is possible that these results could be due to a "ceiling effect" on measurement produced by high doses of apomorphine (1 and 3 mg/kg) (see Fig. 3). For example, at these doses, animals spend approximately 85–100% of their time in stereotyped sniffing behavior. However, Rosengarten and Friedhoff [22] have previously reported that intraperitoneal administration of a high dose of haloperidol prenatally decreases neuroleptic binding in caudate and decreases responsiveness to a test dose of apomorphine (0.3 mg/kg), while such treatment postnatally produces an opposite response pattern—an increase in caudate neuroleptic binding and an increase in sensitivity to 0.3 mg/kg apomorphine. In the present study, the treatment began prenatally and continued postnatally. Thus, one could argue that the postnatal treatment may partially offset the effects of the prenatal treatment, and may result in a lack of an altered sensitivity to high doses of apomorphine in the treated animals.

Although in this study we observed that haloperidol-treated offspring did not differ from control animals in their sensitivity to high doses of apomorphine, in a previous study [23] we observed that such treated offspring were less sensitive to the behavioral effects of amphetamine. Amphetamine is an indirect catecholamine agonist, acting presynaptically to increase dopamine and norepinephrine release and to prevent reuptake of these catecholamines into the presynaptic terminals [12]. Apomorphine, a more specific agonist of the dopamine system, presumably directly activates dopamine receptors [9], predominately postsynaptic receptors in high doses [6]. Differences in the behavioral responsiveness to these two agonists may have been due to drug differences in the relative potency for stimulation of the dopamine and norepinephrine systems. An alternative hypothesis is that the chronic treatment may have selectively affected presynaptic rather than postsynaptic neural components of the dopamine system, which would be reflected by the observed hyposensitivity to the indirect agonist amphetamine but normal sensitivity to high doses of the direct agonist apomorphine. This hypothesis would also be consistent with the observed hyposensitivity of treated offspring to low doses of apomorphine, presumably reflecting a deficiency (or hyposensitivity) of regulatory presynaptic autoreceptors.

At P65, haloperidol-treated offspring exhibited significantly more catalepsy than control offspring in response to cholinergic stimulation by 2 and 5 mg/kg arecoline. These results indicate a behavioral supersensitivity of the cholinergic system to pharmacological stimulation. This supersensitivity might be a trans-synaptic effect of a subsensitive dopamine system resulting from early chronic treatment with haloperidol. Dopaminergic innervation in the striatum is thought to exert an inhibitory influence on acetylcholine interneurons [5, 16, 21]. If the dopamine system is itself subsensitive to stimulation, then perhaps this would result in a release of the cholinergic neurons from dopaminergic inhibition, and would lead to a hypersensitivity of these cholinergic neurons. Conversely, in the adult, chronic haloperidol pretreatment has been shown to result in both dopamine supersensitivity and cholinergic hyposensitivity [7,10].

Table 1 summarizes the psychopharmacological effects of chronic dopamine receptor blockade with neuroleptics in adult and developing animals. Animals treated during development show a pattern of psychopharmacological responses that is opposite that found among animals treated with neuroleptics in adulthood. In neurochemical terms, moreover, prenatal haloperidol administration has been reported to decrease dopamine receptor binding in caudate, while haloperidol administration postnatally or in adulthood has resulted in an increase in dopamine receptor binding [17,22]. From such psychopharmacological and neurochemical evidence, it appears that compensatory processes occurring during development in response to chronic drug treat-

TABLE 1

PSYCHOPHARMACOLOGICAL EFFECTS OF CHRONIC DOPAMINE RECEPTOR BLOCKADE WITH NEUROLEPTICS IN ADULT AND DEVELOPING ANIMALS

Psychopharmacological sensitivity to:	Adult chronic treatment	Infant chronic treatment
Amphetamine (a dopamine agonist)	Supersensitivity [22]	Hyposensitivity [21]
Haloperidol (a DA antagonist)	Hyposensitivity [1]	Supersensitivity [21]
Arecoline (a cholinergic agonist)	Hyposensitivity [5,8]	Supersensitivity (present study)
Low doses of apomorphine (presumably stimulating autoreceptors)	Supersensitivity (measured neuropharmacologically) [17]	Hyposensitivity (present study)

ment are different from those occurring in adulthood. In the autonomic nervous system the existence of a viable postsynaptic receptor has been shown to be important for the maintenance of incoming afferents (presynaptic terminals) [20]. Perhaps the same holds for the CNS, so that chronic blockage of dopamine postsynaptic receptors may lead to degeneration of some of the in-growing dopaminergic presynaptic terminals. This might explain the decrease in the ability of amphetamine to stimulate the dopamine system [23], and the apparent subsensitivity of dopamine autoreceptors, which are in part located on dopamine presynaptic afferents of nigrostriatal and mesolimbic brain regions [6]. A loss of some of the dopamine afferents on acetylcholine interneurons could lead to a loss of some of the inhibitory input on these neurons, resulting in an apparent increase in functional activity and sensitivity for stimulation. Clearly, more work is needed to elucidate regulatory processes that occur during development. Such work is necessary to determine the principles by which brain maturation is affected by psychoactive agents and environmental events.

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