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Chronic haloperidol during development attenuates dopamine autoreceptor function in striatal and mesolimbic brain regions of young and older adult rats*

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Abstract. The effects of chronic haloperidol administration during the prenatal and preweanling periods on dopamine autoreceptor function were examined in striatum, olfactory tubercles, and nucleus accumbens of young (2–3 month) and older (12–13 month) adult rats. In striatum of young and older adult rats that had been chronically treated with haloperidol early in life, as well as in the nucleus accumbens of older adults receiving early chronic haloperidol, gamma-butyrolactone (GBL) did not induce significant increases in dopamine levels. In olfactory tubercles of young adults that had received early chronic treatment with haloperidol, apomorphine pretreatment failed to reverse the observed GBL-induced increase in dopamine levels. Thus, dopamine autoreceptor function appears to be attenuated in rats chronically treated with haloperidol during early development, in contrast to reports of autoreceptor supersensitivity following neuroleptic treatment in adulthood.

Key words: Ontogeny – Haloperidol – Dopamine autoreceptors – Striatum – Nucleus accumbens – Olfactory tubercles – Gamma-butyrolactone – Apomorphine – Dopamine

Chronic haloperidol treatment during development has been shown to have pronounced behavioral, psychopharmacological, and neurochemical effects. Animals treated chronically with haloperidol throughout the prenatal and preweanling periods have been observed to be hyperactive in young adulthood and to exhibit an increase in hole-poke behavior when compared with age-matched controls (Spear et al. 1980). These animals are also less sensitive to amphetamine in terms of increases in open field activity and more sensitive to haloperidol-induced catalepsy when compared with control animals (Spear et al. 1980). Animals chronically treated with haloperidol early in life have also been shown to exhibit decreased adenylate cyclase activity (Lerner and Nose 1977) and alterations in neuroleptic binding (Rosengarten and Friedhoff 1979).

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Shalaby and Spear (1980) observed that young adults that had been chronically treated with haloperidol until weaning exhibited an attenuated low dose (0.05 mg/kg) suppressant effect of apomorphine on locomotor activity, an effect that is presumably mediated by presynaptic dopamine (DA) autoreceptors (e.g., see DiChara et al. 1978). Chronic treatment with haloperidol early in life, therefore, appears to induce alterations in presynaptic DA neuronal activity that may contribute to the pattern of observed alterations in behavioral and psychopharmacological responses induced by this behavioral teratogen.

Although the results of Shalaby and Spear (1980) suggest that chronic treatment with haloperidol early in life may disrupt DA autoreceptors mediating the low dose suppressant effect of apomorphine, it is not clear from these psychopharmacological results whether this presumed attenuation in DA autoreceptor function is restricted to a particular terminal region or whether it might reflect a general disruption of autoreceptor activity in multiple DA terminal areas.

There are a variety of means by which DA autoreceptor function can be examined within specific DA terminal regions. One such technique that has been frequently used to investigate DA autoreceptor function in striatal and mesolimbic terminal regions involves assessing the neuropharmacological effects of gamma-butyrolactone (GBL) (see Roth 1979 for a review). GBL interrupts impulse flow in DA neurons (e.g., Walters and Roth 1974), preventing DA release and therefore decreasing stimulation of presynaptic autoreceptors (see Roth 1979). This in turn leads to an increase in synthesis and accumulation of DA in the terminal regions, which can be reversed by pretreatment with apomorphine (e.g., Nowycky and Roth 1978). It would be expected that a disruption of autoreceptor function would be characterized by an attenuation or a lack of an apomorphine-induced reversal of the effects of GBL upon DA levels, and perhaps even a diminution of the GBL-induced increase in DA levels themselves.

In the present experiment, the GBL technique was used to investigate the effects of chronic haloperidol treatment during development on presynaptic DA autoreceptor function in specific DA terminal regions of striatum, olfactory tubercles, and nucleus accumbens of young as well as older adult animals. Animals given chronic haloperidol treatment early in life have typically been examined only into young adulthood, a period when behavioral and psychopharmacological alterations are quite evident. There has been little investigation of the behavioral, psychopharmacological or neuropharmacological re-

sponses of these animals later in life. In light of recent emphasis on the importance of time of testing after developmental administration of neuroteratogens (see Adams and Buelke-Sam 1981; Spear 1984; Spyker 1975), it seems important to examine the long-term impact of chronic haloperidol treatment during development in older as well as young adult animals. Consequently, in this experiment, DA autoreceptor function was examined in specific DA terminal regions in young (2–3 month) and older (12–13 month) adult rats following chronic treatment with haloperidol or saline during the prenatal and preweanling periods.

Methods

Subjects and chronic drug treatment. Pairs of Sprague-Dawley derived albino rats were placed into standard plastic breeding cages, and daily vaginal smears were taken. Day 1 of gestation was defined as the 1st day upon which sperm were detected in a vaginal smear, and on this day the male was removed from the home cage. From the 1st day of gestation until weaning of the offspring on postnatal day 21, twice daily SC (nape of neck) injections of 0.25 mg/kg haloperidol (courtesy of McNeil Pharmaceutical) or 0.9% saline were given to the pregnant and lactating females at 09:00 h and 21:00 h. Animals were maintained on a 12-h light/dark cycle (lights on at 07:00 h) with free access to food (Purina Rat Chow) and water. A dam was not disturbed, and an injection not given, if the dam was in the process of giving birth. Litters were culled to 10 pups within 24 h of birth, with litters of less than eight offspring not being used in this experiment. At the time of weaning, litters were group housed with littermates of the same sex.

Neurochemical analyses. At 2–3 months or 12–13 months postnatally, offspring were placed into one of the following three treatment groups prior to sacrifice and subsequent neurochemical analysis: 1 mg/kg apomorphine hydrochloride (APO) followed by 750 mg/kg/ml gamma-butyrolactone (GBL); 0.2% ascorbate (ASC) vehicle followed by GBL; ASC followed by 0.9% saline (SAL). APO or its ASC vehicle was given 40 min prior to sacrifice, and GBL or its SAL vehicle were given 35 min before sacrifice. Animals were sacrificed between 11:00 and 17:00 h. Striatum, olfactory tubercles, and nucleus accumbens were dissected (see Springer et al. 1981 for dissection procedure), frozen on dry ice and stored at −75° C for less than 1 week prior to assay. DA was isolated according to the procedures of Earley and Leonard (1978) and assayed fluorometrically according to Pohorecky's (1978) modifications of the method of Chang (1964). Protein determinations were conducted by the method of Lowry (1951).

Results

Baseline DA levels. Preliminary analyses revealed no significant sex differences in the neurochemical data, hence the data were collapsed across sex prior to the analyses described below.

A 2 (Chronic Treatment) X 2 (Age) analysis of variance (ANOVA) was conducted on DA levels of ASC/SAL treated animals within each brain region in order to assess the effects of chronic haloperidol treatment and age on DA levels (see Table 1). In each brain region a significant effect of Age was observed with the older animals exhibiting greater levels of DA than the young adults [for striatum, $F(1,32) = 35.09$, $P < 0.001$; for olfactory tubercles, $F(1,32) = 45.28$, $P < 0.001$; for nucleus accumbens, $F(1,31) = 31.65$; $P < 0.001$]. In olfactory tubercles there was also a significant effect of Chronic Treatment [$F(1,32) = 6.66$, $P < 0.025$], reflecting that chronic haloperidol-treated animals exhibited lower DA levels in olfactory tubercles when compared to their saline controls. In nucleus accumbens, a significant Treatment × Age interaction [$F(1,31) = 15.86$, $P < 0.001$] was observed. A Tukey-A post-hoc test revealed that in this brain region, animals chronically treated with haloperidol

Table 1. DA Levels (ng/mg protein) of young and older adult control (ASC/SAL) groups in striatum, olfactory tubercles, and nucleus accumbens (± SEM)

	Young Adult		Older Adult	
	Saline	Haloperidol	Saline	Haloperidol
Striatum	84.26 (15.47)	58.72 (8.23)	151.61 (14.36)	160.81 (18.61)
Olfactory tubercles	27.89 (4.14)	17.59 (0.89)	56.10 (7.16)	45.06 (4.21)
Nucleus accumbens	42.69 (9.61)	24.80 (2.54)	55.55 (6.52)	51.62 (5.70)

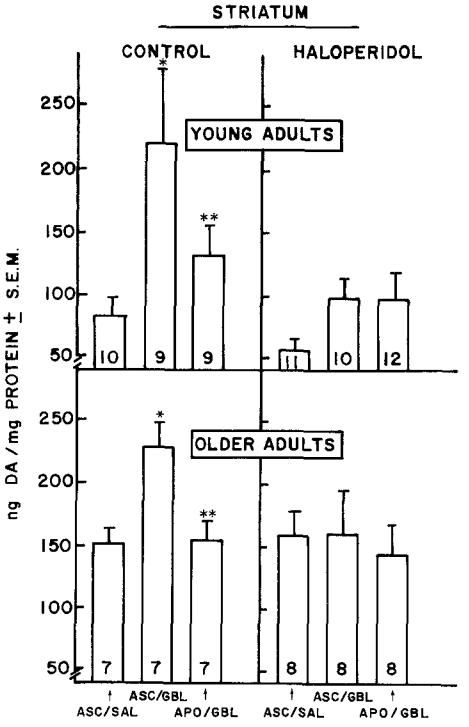

Fig. 1. Dopamine levels following the various drug treatments in striatum of young and older adults chronically treated early in development with saline (control) or haloperidol. Numbers within the bars represent the number of animals in each treatment condition. * Significantly different from ASC/SAL control. ** Significantly different from ASC/GBL group

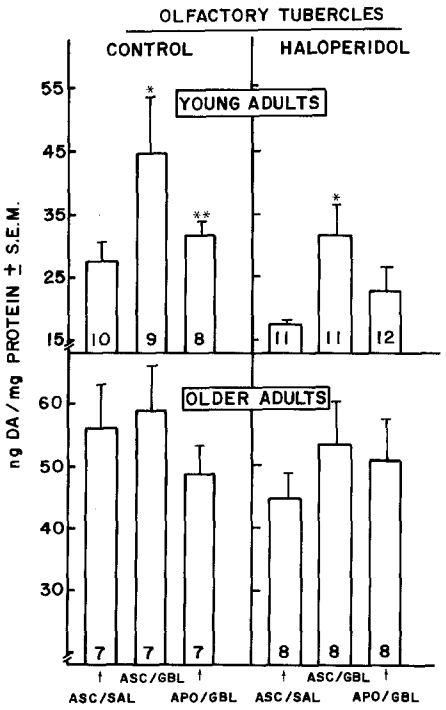

Fig. 2. Dopamine levels following the various drug treatments in olfactory tubercles of young and older adults chronically treated early in development with saline (control) or haloperidol. Numbers within the bars represented the number of animals in each treatment condition. * Significantly different from ASC/SAL control. ** Significantly different from ASC/GBL group

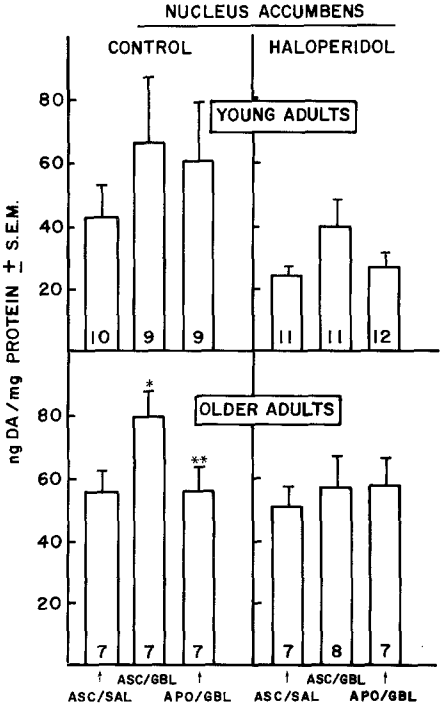

Fig. 3. Dopamine levels following the various drug treatments in nucleus accumbens of young and older adults chronically treated early in development with saline (control) or haloperidol. Numbers within the bars represent the number of animals in each treatment condition. * Significantly different from ASC/SAL control. ** Significantly different from ASC/GBL group

and sacrificed as young adults were characterized by significantly lower DA levels than control animals sacrificed as older adults.

DA autoreceptor function. Given the substantial differences in baseline DA levels observed between young and older adults within each brain region, a 3 (Drug) × 2 (Chronic Treatment) ANOVA was performed at each age to examine autoreceptor function within each of the three DA terminal regions. Planned comparisons ($P < 0.05$) were used to examine the two comparisons of interest: (a) to assess possible GBL-induced increases in DA levels, DA levels in the ASC/GBL group were compared with those of the control (ASC/SAL) group; (b) in instances where GBL induced an increase in DA levels, the efficacy of apomorphine for attenuating this increase was assessed by comparing DA levels between the ASC/GBL and APO/GBL groups.

In the striatum (see Fig. 1) of chronically-treated control animals at both ages, GBL induced significant increases in DA. These increases were significantly attenuated by apomorphine pretreatment, indicating fully functional autoreceptors. However, in animals chronically treated with haloperidol no significant increase in DA was observed following GBL at either age.

In olfactory tubercles, young adults chronically treated with either saline or haloperidol exhibited a significant increase in DA following GBL administration. As can be seen in Fig. 2, this increase was significantly attenuated by apomorphine only in the animals chronically treated with saline. Older animals that had received either chronic treatment exhibited no significant increase in DA following GBL administration in the olfactory tubercles.

In nucleus accumbens (see Fig. 3), no significant GBL-induced increase in DA was observed in young animals under either treatment condition. However, animals chronically treated with saline and sacrificed in older adulthood exhibited a significant increase in DA following GBL, an increase that was significantly attenuated by apomorphine. No indication of DA autoreceptor function was observed in the nucleus accumbens of older adult animals that had been chronically treated with haloperidol early in life.

Table 2. Mean body weights in grams for male and female chronically treated animals (± SEM)

	Male		Female	
	Saline	Haloperidol	Saline	Haloperidol
Young	247(8)	242(7)	186(3)	173(4)
Old	588(16)	514(15)*	338(14)	300(10)*

* Significantly different from saline control

Body weights. Older adults chronically treated with haloperidol early in life weighed less than their aged-matched controls (see Table 2) [for males, $F(1,16) = 6.41$, $P < 0.025$; for females, $F(1,26) = 4.64$, $P < 0.05$]. This effect was not seen in animals sacrificed in young adulthood.

Discussion

In the present study, DA autoreceptor function was observed to be impaired in striatum, olfactory tubercles and nucleus accumbens of animals treated chronically with haloperidol during development. Thus, chronic haloperidol treatment early in life appears to disrupt DA autoreceptor function in both mesolimbic and striatal DA terminal regions. Baseline DA levels were also decreased by early chronic treatment with haloperidol in the olfactory tubercles and nucleus accumbens of young adults, as well as the olfactory tubercles of animals sacrificed in older adulthood. Chronic developmental treatment with haloperidol was also observed to decrease body weight in animals sacrificed as older, but not younger, adults. These body weight alterations do not appear to be directly related to the neurochemical alterations seen in the treated animals, given that the treatment-related decreases in body weight were only seen in the older adults, whereas neurochemical alterations were seen in both younger and older mature animals.

The results of the present study provide neuropharmacological support for the suggestion of Shalaby and Spear (1980) that DA autoreceptors may be hyposensitive in animals treated chronically with haloperidol during development, a suggestion based on the observation that treated animals were insensitive to the locomotor suppressant effects of low doses of apomorphine. This pattern of DA autoreceptor hyposensitivity seen in all three brain regions following haloperidol administration early in life is opposite that observed after chronic neuroleptic treatment in adulthood. For instance, Nowycky and Roth (1978) observed that apomorphine was more potent in blocking GBL-induced increases in DOPA accumulation in striatum of adult animals treated with the depot neuroleptic, fluphenazine decanoate, than in striata from control animals. Indeed, a number of neuropharmacological studies have reported that DA autoreceptors in striatal and mesolimbic DA regions appear to be supersensitive following adult chronic treatment with neuroleptics including haloperidol (e.g., see Roth 1979 for a review). Chronic pre- and postnatal treatment with neuroleptics has also been reported to produce opposite effects from those observed following chronic neuroleptic treatment in adulthood when examining the psychopharmacological response profile to drugs affecting the dopaminergic system. After adult chronic treatment with neuroleptics, animals are less sensitive to a test dose of haloperidol (Asper et al. 1973), but exhibit supersensitivity to the catecholaminergic agonist, amphetamine (Gianutsos et al. 1978; Thornburg and Moore 1975). Conversely, after chronic pre- and postnatal neuroleptic treatment, animals are supersensitive to haloperidol and exhibit a lessened sensitivity to amphetamine (Spear et al. 1980) Thus, it appears that the long-term alterations induced by chronic treatment with neuroleptics early in life are different from, and indeed often opposite to, the compensatory adaptations occurring in response to chronic neuroleptic treatment in adulthood.

In the present study, the drug treatment was given throughout gestation and the nursing period and thus, from these results alone, it is not possible to determine the critical period for these effects. Yet, it appears that treatment during the prenatal period may be most critical in producing attenuated autoreceptor responsivity, given that when neuroleptic treatment is restricted to the postnatal period a treatment-induced attenuation of DA autoreceptor activity is not seen, at least when using sensitivity to the low dose suppressant effect of apomorphine as an index of DA autoreceptor activity. Cuomo et al. (1983) observed that chronic postnatal treatment with haloperidol did not influence the low dose suppressant effect of apomorphine upon locomotor activity, although the effects of a larger dose of apomorphine were more marked in the chronically-treated animals than in controls. These latter results are consistent with those of Rosengarten and Friedhoff (1979), where they observed that animals treated chronically with haloperidol during the nursing period exhibited increased apomorphine-induced stereotyped behavior along with increased tritiated spiroperidol binding to striatal DA receptors, effects that are similar to those seen following chronic treatment with neuroleptics in adulthood. Most interestingly, Friedhoff and associates conversely observed an opposite profile of decreased apomorphine-induced stereotyped behavior and decreased striatal DA receptor binding when haloperidol was administered prenatally rather than postnatally (Rosengarten and Friedhoff 1979), with the critical period for these effects apparently occurring during gestational days 15–18 (Rosengarten et al. 1983). Thus, it appears that whereas chronic neuroleptic treatment during the early postnatal period produces adaptations within the dopaminergic system that are similar to those seen after treatment in adulthood, prenatal treatment alone, or combined pre- and postnatal treatment, produces long-term alterations in the dopaminergic system that are opposite in nature to the compensatory processes occurring in response to chronic neuroleptic treatment in adulthood.

It is not known how chronic treatment with neuroleptics early in life could produce long-term alterations in the dopaminergic system that often appear to be functionally the converse of compensatory adaptations occurring in response to chronic administration of neuroleptics in adulthood. In the autonomic nervous system, the existence of viable postsynaptic receptors has been shown to be important early in development for the maintenance of afferent terminals (Purves and Lichtman 1978). Perhaps a similar phenomenon is seen in the developing central nervous system, so that chronic blockade of DA postsynaptic receptors may lead to a reduction in dopaminergic terminal projections. This might lead to an attenuation in the apparent activity of DA presynaptic autoreceptors and perhaps a decrease in DA levels in certain terminal regions (effects observed in the present study) along with a long-term down-regulation of the number of postsynaptic DA receptors (Rosengarten and Friedhoff 1979; Rosengarten et al. 1983) and an attenuation in responsiveness to DA agonists (Rosengarten and Friedhoff 1979; Spear et al. 1980).

Although in this study, chronic haloperidol administration during development was observed to disrupt DA autoreceptor function in all three brain regions whenever signs of autoreceptor function were seen in control animals, the GBL technique did not reveal any positive indications of DA autoreceptor function in the olfactory tubercles of older adult control animals and in the nucleus accumbens of young adult controls. Given that the examination of any potential treatment-related alterations in DA autoreceptor

function is predicated by the necessity of observing signs of autoreceptor function in the target brain regions of control animals, it was therefore not possible to examine treatment-induced disruptions of autoreceptor function in these two instances using the GBL technique in the present study. It is possible that other, potentially more sensitive, measures of DA autoreceptor function might reveal consistent signs of autoreceptor function across age in mesolimbic as well as in striatal brain regions. For instance, assessing the influence of DA agonists on rates of DA synthesis by examining the rate of incorporation of tritiated tyrosine into DA (e.g., Westfall et al. 1983) or by measuring the accumulation of DOPA after decarboxylase inhibition (e.g., Roth 1979) might produce indications of autoreceptor function consistently across age of adult animals in mesolimbic brain regions, and thus may be more appropriate for assessing treatment-induced alterations in DA autoreceptor function in future investigations.

It is not clear why age-related differences in signs of mesolimbic autoreceptor function were observed when using the GBL technique. Autoreceptor function has been more extensively studied in striatum (e.g., Demarest et al. 1983; Bannon et al. 1981; Gudelsky and Moore 1976), than in mesolimbic brain regions, although little attention has been directed to possible alterations in DA autoreceptor function with age of mature animals within any brain region. There is some discrepancy as to whether signs of autoreceptor function are seen in nucleus accumbens using the GBL technique. For instance, Beart and Gundlach (1980) found that GBL had no effect on 3,4-dihydroxyphenylacetic acid (DOPAC) levels in nucleus accumbens although a GBL-induced decrease in DOPAC levels was seen in striatum. Similarly, Lawson et al. (1981) found no effect of GBL or amphetamine on DA synthesis in nucleus accumbens, although both treatments increased synthesis in striatum. However, in a later report (Demarest et al. 1983) this same group of researchers conversely reported that GBL did affect synthesis in nucleus accumbens. Indeed, it has been reported that olfactory tubercles and nucleus accumbens are equally sensitive to the ability of GBL to induce increases in DA synthesis, although less sensitive when compared to striatum (Anden et al. 1983; Demarest et al. 1983). It is possible that some of the discrepancies concerning the presence or absence of DA autoreceptors in nucleus accumbens when using the GBL technique may be related to differences in the age of the animals that were examined, given the present results of marked age differences within adult animals regarding signs of autoreceptor function following GBL and apomorphine treatment in nucleus accumbens as well as the olfactory tubercles.

Although it is not clear as to why there are these age-dependent alterations in signs of autoreceptor function in mesolimbic brain regions when using the GBL technique, a number of possibilities are apparent. There may be differential baseline rates of synthesis or release of DA in these mesolimbic brain regions that vary with age and that may obscure indications of autoreceptor function using the GBL technique in nucleus accumbens of young adult rats and the olfactory tubercles of older adult rats. It is also possible that there may be regionally specific alterations with age in sensitivity to GBL. Although the mechanisms by which GBL produces a blockade of impulse flow in dopaminergic neurons is unknown, it has been suggested that GBL may act though the stimulation of GABAergic inhibitory mechanisms (e.g., see Biswas and Carlsson 1977; Liljequist and Engel 1980). There are numerous reports of age-related alterations in levels of GABA, GABA receptor binding, and GABA interactions with benzodiazepine receptor binding in various brain regions (e.g., see Calderini et al. 1981) that could possibly contribute to the alterations in GBL sensitivity within these brain regions with age. Whether the GBL results obtained in this experiment are related to one or more of these possibilities, or whether they indeed reflect age-related shifts in autoreceptor activity in mesolimbic brain regions, is a matter for further investigation.

Age-related alterations were also seen in baseline DA levels, with greater levels of DA being seen in 12–13-month-old than 2–3-month-old adult rats. These findings of age-related increases in DA levels were somewhat surprising, given numerous reports of decreases in dopaminergic activity with age (e.g., see Govoni et al. 1978; Hicks et al. 1980; Strong et al. 1982). Yet, many of the age-related decreases in dopaminergic function were reported in senescent rats older than 2 years of age (e.g., Govoni et al. 1978; Hicks et al. 1980; Strong et al. 1982), an age well beyond those of the older, but clearly not senescent, 12–13-month-old adult rats examined in the present study. For instance, Strong et al. (1982) examined DA levels in various striatal regions of 6-, 16-, and 26-month-old rats, and observed that significant decreases in DA levels were generally seen at 26 months, but not at 16 months. Indeed, in their experiment, there were trends towards an increase in DA levels between 6 and 16 months of age in some of the striatal regional slices. Using baseline neurotransmitter levels as an index, the dopaminergic system has been reported to be the slowest to mature of the monoamine systems, with DA levels at 40 days of age being only 75% of the levels of DA seen at 12 months of age in the rat (Agrawal et al. 1966). Thus, it is possible that the increases in DA seen between 2–3 and 12–13 months postnatally in the present study may reflect rather delayed ontogenetic increases in DA levels that occur prior to a subsequent decline in levels of DA later in the lifespan.

The results of the present study in conjunction with previous research (e.g., Rosengarten and Friedhoff 1979; Rosengarten et al. 1983; Shalaby and Spear 1980; Spear et al. 1980) suggest that long-term alterations occurring in response to chronic neuroleptic treatment early in development are to a large extent functionally converse to the compensatory processes occurring in response to neuroleptic treatment later in life. Further work directed towards elucidating regulatory processes that occur during development is needed to determine principles by which psychoactive drugs and environmental events influence maturational processes within the developing central nervous system.

References

Adams J, Buelke-Sam J (1981) Behavioral assessment of the postnatal animal: testing and methods development. In: Kimmel CA, Buelke-Sam J (eds) Developmental Toxicology. Raven Press, New York, pp 223–258

Agrawal HC, Glisson SN, Himwich WA (1966) Changes in monoamines of rat brain during post-natal ontogeny. Biochem Biophys Acta 130: 511–513

Anden N, Grabowska-Anden M, Lindgren S, Thornstrom U (1983) Synthesis rate of dopamine: difference between corpus striatum and limbic system as a possible explanation of variations in reactions to drugs. Naunyn-Schmiedeberg's Arch Pharmacol 323: 193–198

Asper H, Baggiolini M, Burki H, Lauener H, Ruch W, Stille G (1973) Tolerance phenomena with neuroleptics: Catalepsy, apomorphine stereotypies and striatal dopamine metabolism after single and repeated administration of loxapine and haloperidol. Eur J Pharmacol 22: 287–294

Bannon MJ, Michaud RL, Roth RH (1981) Mesocortical dopamine neurons: lack of autoreceptors modulating dopamine synthesis. Mol Pharmacol 19: 270–275

Beart PM, Gundlach AL (1980) 3,4-dihydroxyphenylacetic acid (DOPAC) and the rat mesolimbic dopaminergic pathway: drug effects and evidence for somatodendritic mechanisms. Br J Pharmacol 69: 241–247

Biswas B, Carlsson A (1977) The effect of intracerebroventricularly administered GABA on brain monoamine metabolism. Naunyn-Schmiedeberg's Arch Pharmacol 299: 41–46

Calderini G, Bonetti AC, Aldino A, Savoini G, Di Perri B, Biggio G, Toffano G (1981) Functional interaction between benzodiazepine and GABA recognition sites in aged rats. Neurobiol Aging 2: 309–313

Chang CC (1964) A sensitive method for spectrophotofluormetric assay of catecholamines. Int J Pharmacol 3: 643–649

Cuomo V, Cattabeni F, Racagni G (1983) The influence of early postnatal treatment with haloperidol on the effects induced by small and large doses of apomorphine on locomotion of adult rats. Neuropharmacology 22: 1137–1139

Demarest KT, Lawson-Wendling KL, Moore KE (1983) D-amphetamine and gamma-butyrolactone alteration of dopamine synthesis in the terminals of nigrostriatal and mesolimbic neurons. Biochem Pharmacol 32: 691–697

Di Chiara G, Corsini GU, Mereu GP, Tissari A, Gessa GL (1978) Self-inhibitory dopamine receptors: their role in the biochemical and behavioral effects of low doses of apomorphine. In: Roberts PJ et al. (eds) Advances in Biochemical Psychopharmacology, vol 19. Raven Press, New York, pp 275–292

Earley CJ, Leonard BE (1978) Isolation and assay of noradrenaline, dopamine, 5-hydroxy-tryptamine, and several metabolites from brain tissue using disposable Bio-Rad columns packed with Sephadex G-10. J Pharmacol Meth 1: 67–79

Gianutsos G, Hynes M, Drawbaugh R, Lal H (1978) Similarities and contrasts between the effects of amphetamine and apomorphine in rats chronically treated with haloperidol. Prog Neuropsychopharmacol 2: 161–167

Govoni S, Spano PF, Trabucchi M (1978) [3H]-Haloperidol and [3H]spiroperidol binding in rat striatum during aging. J Pharm Pharmacol 30: 448–449

Gudelsky GA, Moore KE (1976) Differential drug effects on dopamine concentrations and rates of turnover in the median eminence, olfactory tubercle and corpus striatum. J Neural Transm 38: 95–105

Hicks P, Strong R, Schoolar JC, Samorajski T (1980) Aging alters amphetamine-induced stereotyped gnawing and neostriatal elimination of amphetamine in mice. Life Sci 27: 715–722

Lawson K, Demarest K, Moore K (1981) Differences in the effects of d-amphetamine and gamma-butyrolactone on dopamine synthesis in striatum and nucleus accumbens. Fed Proc 40: 312

Lerner P, Nose P (1977) Haloperidol: effect of long-term treatment on rat striatal dopamine synthesis and turnover. Science 1: 181–183

Liljequist S, Engel J (1980) Effect of ethanol on central gabaergic mechanisms. In: Eriksson K et al. (eds) Animal Models in Alcohol Research. Academic Press, London, pp 309–315

Lowry OH, Rosenbrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. J Biol Chem 193: 266–275

Nowycky MC, Roth RH (1978) Dopaminergic neurons: role of presynaptic receptors in the regulation of transmitter biosynthesis. Prog Neuro-Psychopharmacol 2: 139–158

Pohorecky L, Newman B, Sun J, Bailey W (1978) Acute and chronic ethanol ingestion and serotonin metabolism in rat brain. J Pharmacol Exp Ther 204: 424–443

Purves D, Lichtman J, (1978) Formation and maintenance of synaptic connections in autonomic ganglia. Physiol Rev 58: 861–862

Rosengarten H, Friedhoff A (1979) Enduring changes in dopamine receptor cells of pups from drug administration to pregnant and nursing rats. Science 203: 1133–1135

Rosengarten H, Friedman E, Friedhoff AJ (1983) Sensitive period for the effect of haloperidol on development of striatal dopamine receptors. In: Haber B, Perez-Polo SR, Hashim GA, Stella AMG, Paul NW (eds) Nervous System Regeneration. Birth Defects: Original Article Series, *Volume 19,* Number 4, Allan R. Liss, Inc., New York, pp 511–513

Roth RH (1979) Dopamine autoreceptors: pharmacology, function and comparison with post-synaptic dopamine receptors. Commun Psychopharmacol 3: 429–445

Shalaby IA, Spear LP (1980) Chronic administration of haloperidol during development: later psychopharmacological responses to apomorphine and arecoline. Pharmacol Biochem Behav 13: 685–690

Spear LP (1984) Age at the time of testing reconsidered in neurobehavioral teratological research. In: Yanai J (ed) Neurobehavioral Teratology, Elsevier Science Publishers, Amsterdam, pp 315–328

Spear P, Shalaby IA, Brick J (1980) Chronic administration of haloperidol during development: behavioral and psychopharmacological effects. Psychopharmacology 70: 47–58

Springer J, Hannigan Jr JH, Isaacson RL (1981) Changes in dopamine and DOPAC following systemic administration of apomorphine and 3,4-dihydroxyphenylamino-2-imidazoline (DPI) in rats. Brain Res 220: 226–230

Spyker JM (1975) Assessing the impact of low level chemicals on development: behavioral and latent effects. Fed Proc 34: 1835–1844

Strong R, Samorajski T, Gottesfeld Z (1982) Regional mapping of neostriatal neurotransmitter systems as a function of aging. J Neurochem 39: 831–836

Thornburg J, Moore K (1975) Supersensitivity to dopaminergic agonists induced by haloperidol. NIDA Research Monograph Series 3: 23–28

Walters JR, Roth RH (1974) Dopaminergic neurons: drug-induced antagonism of the increase in tyrosine hydroxylase activity produced by cessation of impulse flow. J Pharmacol Exp Ther 191: 82–91

Westfall TC, Naes L, Paul C (1983) Relative potency of dopamine agonists on autoreceptor function in various brain regions of the rat. J Pharmacol Exp Ther 224: 199–205

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