Pharmacology Biochemistry & Behavior, Vol. 20, pp. 575–581, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Estradiol Application to One Striatum Produces Postural Deviation to Systemic Apomorphine

JEFFREY N. JOYCE[1] AND CAROL VAN HARTESVELDT[2]

Department of Psychology and the Center for Neurobiological Sciences
University of Florida, Gainesville, FL 32611

Received 8 August 1983

JOYCE, J. N. AND C. VAN HARTESVELDT. *Estradiol application to one striatum produces postural deviation to systemic apomorphine.* PHARMACOL BIOCHEM BEHAV **20**(4) 575–581, 1984.—In order to test whether estrogen acts directly in the dorsal striatum to affect dopamine-mediated behavior, ovariectomized female Long-Evans rats were given a unilateral striatal application of estradiol, injected systemically with apomorphine (APO), and tested for lateralization of stereotypic behaviors. In the first experiment, estradiol, cholesterol, or an empty cannula was inserted and the rat given 0.7 mg/kg APO 1–4 hours later. Rats directed their stereotypic behaviors to the side ipsilateral to the insert of estradiol with dorsal striatal inserts, but not with inserts in ventral striatum or neocortex. Neither cholesterol nor the empty cannula inserts were effective in producing lateralization of the stereotypic behaviors. In the second experiment, intrastriatal inserts of 17 α-estradiol were ineffective in producing a lateralization of APO-induced stereotyped behavior. In the third experiment, several doses of APO (0.07, 0.75 and 3.0 mg/kg) were tested. At the highest dose no lateralization of APO-induced stereotypic behavior was observed. These results strongly suggest that estradiol acts directly in the dorsal striatum to antagonize APO and thus produce a lateralization of stereotypic behaviors (postural deviation).

Striatum Estrogen Membrane receptor Postural deviation Dopamine and estrogen

PREVIOUS research has shown that estradiol administered systemically can affect behaviors elicited by intrastriatal dopamine [12]. However, it is not known where estradiol acts to modify the efficacy of striatal dopamine (DA). In general it is thought that estrogens act through genomic mechanisms to alter neuronal activity [18,21]. However, it has not been possible to identify intracellular receptors for estrogen in the striatum or in midbrain cell bodies with dopaminergic projections to the striatum, using autoradiographic methods [8, 20, 25]. However, localization of steroid receptors using this method is not an infallible guide for determining the location of sites of action of the steroid hormones. For example, although autoradiographic studies have failed to allow visualization of progesterone-containing cells in the ventral tegmental area (e.g., [26]), application of progesterone into this region can modify sexual receptivity in the female mouse and rat [7,19]. In addition, it has been suggested that estrogen has direct cell membrane effects in the striatum [1].

In order to determine whether steroid hormones can directly affect DA-sensitive neurons in the striatum, estradiol was inserted unilaterally into the striatum and apomorphine (APO), a DA-agonist, was administered systemically. We measured the amount of lateralization of APO-induced stereotypic behaviors (postural deviation), because lateralization of behaviors is a sensitive indicator of an alteration of the DA balance between the two striata [10–12]. A decrease in the DA activity in the estradiol-inserted striatum should result in a lateralization of stereotypic behaviors to the side ipsilateral to the insert (ipsilateral postural deviation). We also measured the regional specificity of the effect by inserting estradiol in nearby sites; the potency of the effect by varying the dose of APO; and the specificity of the effect by also testing inserted cholesterol and 17α-estradiol.

GENERAL METHOD

METHOD

Animals

Female Long-Evans hooded rats (n=60) weighed 180–220 g at the beginning of the experiment. They were housed individually and maintained on a 12:12 light:dark cycle (lights ON, 0800–2000). The rats were ovariectomized bilaterally (OVX) under ether (Mallinckrodt) anesthesia 48 hours before stereotaxic implantation of guide cannulae.

[1]Dr. J. N. Joyce was supported during the completion of this research by a predoctoral traineeship (MH 15737) awarded to the Center for Neurobiological Sciences at the University of Florida, Gainesville, FL. Present address for Dr. J. N. Joyce is the Department of Psychobiology, University of California, Irvine, CA 92717.

[2]Requests for reprints should be addressed to C. Van Hartesveldt.

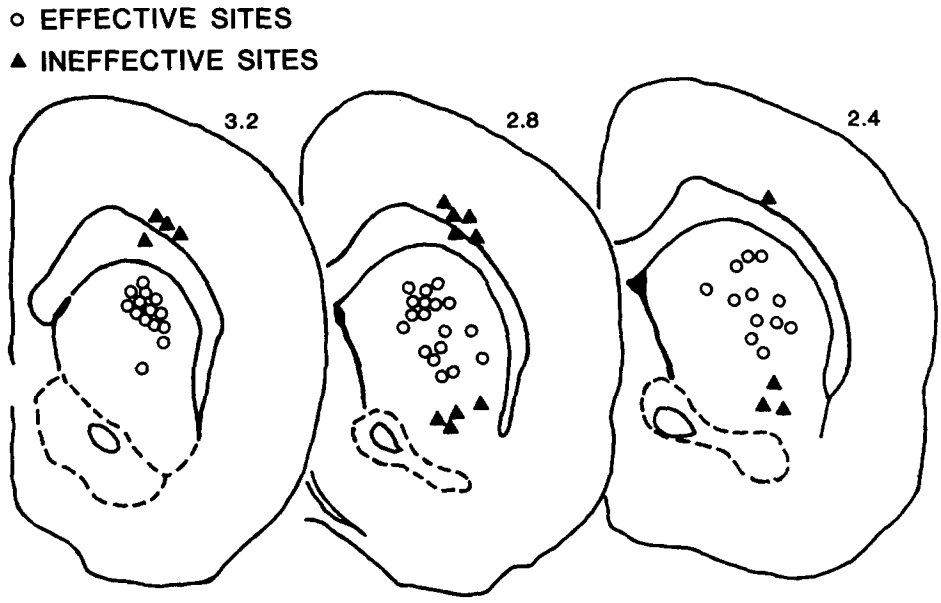

FIG. 1. Location of cannula tips for intracerebral application of a steroid. Open circles indicate placements in dorsal striatum; filled triangles indicate placements outside dorsal striatum.

Stereotaxic Surgery

The OVX rats were implanted bilaterally with permanent cannulae under sodium pentobarbital (W. T. Butler Co.) anesthesia. Guide cannulae were constructed from 21 ga stainless steel tubing and the injection cannulae were constructed using 27 ga tubing. Since the injection cannulae terminated 3.0 mm below the guide cannulae, 43 rats had the guide cannulae stereotaxically implanted such that the injection cannulae were located in the anterior dorsal striatum using the following coordinates derived from Pellegrino *et al.* [23]: +2.0 to 3.0 mm with respect to bregma; 2.0 to 4.0 mm lateral to bregma; 3.5 to 5.0 mm below the surface of the brain. An additional 17 rats had guide cannulae surgically implanted such that the injection cannulae were located either in the ventral striatum or neocortex using the following coordinates derived from Pellegrino *et al.* [23]: +2.0 to 3.4 mm with respect to bregma; 2.0 to 4.0 mm lateral to bregma; 1.5 to 2.0 mm and 6.0 to 7.0 mm below the surface of the brain. Stainless steel stylets, made from closed 27 ga tubing, kept the guide cannulae patent when the 27 ga cannulae were not inserted.

Behavioral Testing

The rats in these experiments were used more than once. The procedure for all experiments is presented below. The steroid to be tested was tapped, under a magnifying lens, into the 27 ga cannula; then the cannula tip was wiped clean with ethanol. The intracerebral application of a hormone was made by inserting the 27 ga cannula, either empty or containing the hormone, through the guide cannula into the brain tissue on one side of the brain. The insertions were made while the rats were restrained, but not anesthetized. The order of insertions was counterbalanced, with a withdrawal period of 5 days between each insert. After each insertion the rats were immediately returned to their home cages. At various times after hormone insertion, the cannula was removed, and the rats were administered APO (IP). After drug administration, the rats were placed into a circular clear Plexiglas observation chamber, 34 cm in diameter and 30.5 cm in height, and observed for 20 min. The duration of postural deviation that occurred both contralaterally and ipsilaterally to the side of intrastriatal insert was recorded continuously by the observer using a two pole switch connected in series to a time clock and a rack of cumulative counters. The cumulative duration of postural deviation was recorded every 5 min for 20 min. The presence or absence of the following classes of behavior (derived from [3,10]) was noted at one min intervals: (1) gnawing; (2) licking; (3) sniffing to a floor or Plexiglas surface; (4) rearing; (5) grooming; (6) locomotion; (7) immobile. All rats used in Experiment 1 were utilized in Experiments 2 and/or 3.

Drugs and Steroids

APO (apomorphine hydrochloride; Sigma) was dissolved in 0.9% saline. The following steroids were used in the powder form: cholesterol (Fisher): estradiol (1,3,5(10)-Estratrien-3,17β-diol; Steraloids); 17α-estradiol (1,3,5(10)-Estratrien-3,17α-diol; Sigma).

Histology

After behavioral testing, rats were administered an overdose of sodium pentobarbital and perfused intracardially with 0.9% saline followed by 10% formalin. The brains were placed in a 20% sucrose-10% formalin mixture 24 hr prior to sectioning. The brains were frozen, sectioned at 30 μm, stained with cresyl violet, and the locations of the cannula tips were verified. Cannula tip placements are shown in Fig. 1.

EXPERIMENT 1

Procedure

OVX rats were given intracerebral inserts of estradiol,

cholesterol and an empty cannula on separate days. Either 1 hour or 4 hours after insertion of the steroid the rats were injected with APO (0.70 mg/kg, IP) for testing. This dose of APO has been shown to produce stereotypic sniffing, lateral head movement and locomotion in unoperated rats [3].

Statistical Analyses

In order to obtain an index of the dominant direction of postural deviation, the time spent ipsilateral was substracted from the time spent contralateral to the side of the intracerebral insert of the steroid (difference score). The difference scores for the total 20 min of the observation period were analyzed for differences due to site of insert (SITE) and steroid inserted (HORMONE). An analysis of covariance was used to determine if the variable SITE (2 levels) and HORMONE (3 levels) had significant overall effects. Because of the split-plot design, between-SITE and within-SITE tests for main effects used different error terms. Between-SITE tests of main effects used the subjects nested within SITE error term, and within DRUG tests of main effects used the within subject error term. Tests for simple main effects were then made using Scheffé's method for multiple comparisons (unequal sample size).

In order to test for differences due to time of insert the difference scores for the total 20 min of the observation period were analyzed for differences due to the steroid inserted (HORMONE) and duration of insert (TIME), using within-subjects comparisons. An analysis of covariance was used to determine if the variable HORMONE (3 levels) nested within TIME (2 levels) had a significant overall effect. Tests for simple main effects were then made using Scheffé's method for multiple comparisons (equal sample size).

RESULTS

Histological analysis of the locations of cannula tips showed that 43 placements were in the dorsal and medial aspect of the caudate-putamen (Fig. 1), the region designated previously as the dorsal striatum [11]. There were 7 placements in the ventral caudate-putamen (ventral striatum), and 10 placements in the neocortex above the striatal placements (Fig. 1). For data analysis the rats were divided into two groups based on the cannula placement, within and outside the dorsal striatum. The injection of APO produced stereotypic sniffing, lateral head movements, and locomotion around the perimeter of the observation chamber. The specific stereotypic behavioral syndrome induced by APO was not altered by insertion of either steroid regardless of the site of implant. Lateralization of these stereotypic behaviors did occur with implants of estradiol into the dorsal striatum.

Rats with estradiol inserted into the dorsal striatum showed APO-induced stereotypies that were directed almost entirely ipsilateral to the side of the intrastriatal insert (Fig. 2-A, $p<0.01$). As indicated by a very small difference score (Fig. 2-A), inserts of cholesterol into the dorsal striatum were no more effective than empty cannula inserts in producing a postural asymmetry of stereotypic behaviors. Inserts of estradiol outside the dorsal striatum were ineffective in producing an asymmetry of APO-induced stereotypic behaviors, as indicated by the small difference score to these inserts (Fig. 2-B). Inserts of estradiol only 0.5 mm dorsal or ventral to the effective sites within the dorsal striatum were ineffective (Fig. 1).

Rats with effective inserts were subsequently tested for the effectiveness of estradiol inserts of 1 hour and 4 hours in duration. As observed previously in these same rats, insertion of estradiol into one striatum for 4 hours resulted in the directing of those stereotypic behaviors ipsilaterally to the side of the insert. The difference score for estradiol was significantly different from empty cannula inserts or cholesterol inserts (Fig. 3-B; $p<0.01$). An insertion of estradiol for 1 hour was as effective as the 4 hour insert in producing asymmetry of stereotypic behaviors to a systemic injection of APO (Fig. 3-A). The lack of effectiveness with 1 hour inserts of cholesterol or an empty cannula is indicated by the small difference scores. Rats used in this experiment were subsequently found to have had cannula sites within the dorsal striatum.

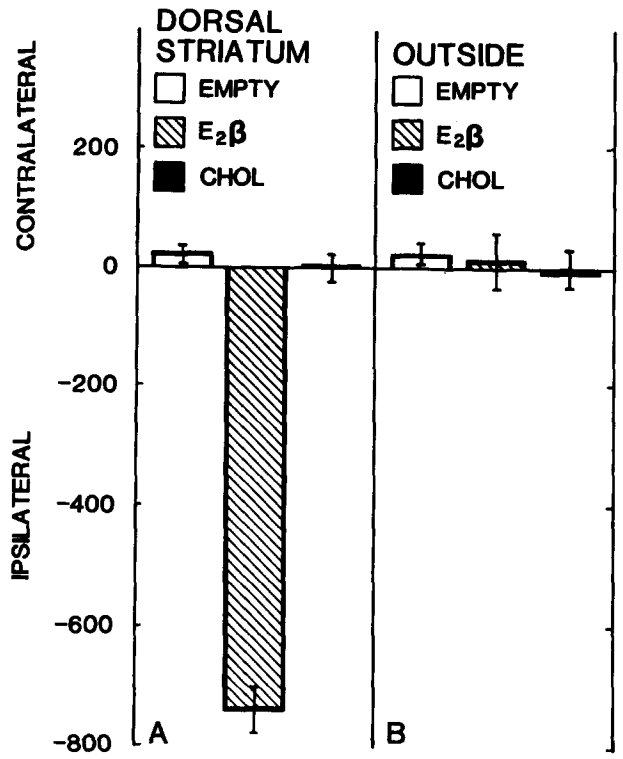

FIG. 2. Behavioral effect of systemically administered APO after intracerebral application of a steroid. The intracerebral application of a steroid was made by inserting an estrogen-filled ($E_2\beta$), cholesterol-filled (CHOL) or empty (EMPTY) cannula through the guide cannula into the brain tissue on one side of the brain. (2-A) Average difference score in response to APO after application of steroid into the dorsal striatum (n=43). The ordinate represents the average difference score for postural deviation expressed in 0.01 min. Ipsilateral deviation was subtracted from contralateral deviation for each animal to obtain an absolute difference score. Positive scores represent a predominantly contralateral deviation, and negative scores, an ipsilateral deviation. The graph represents the mean difference score +/−S.D. for the total observation period. (2-B) Average difference score in response to APO after application of steroid into brain regions outside the dorsal striatum (n=17). The ordinate represents the average difference score for postural deviation expressed in 0.01 min. Ipsilateral deviation was subtracted from contralateral deviation for each animal to obtain an absolute difference score. Positive scores represent a predominantly contralateral deviation, and negative scores, an ipsilateral deviation. The graph represents the mean difference score +/−S.D. for the total observation period.

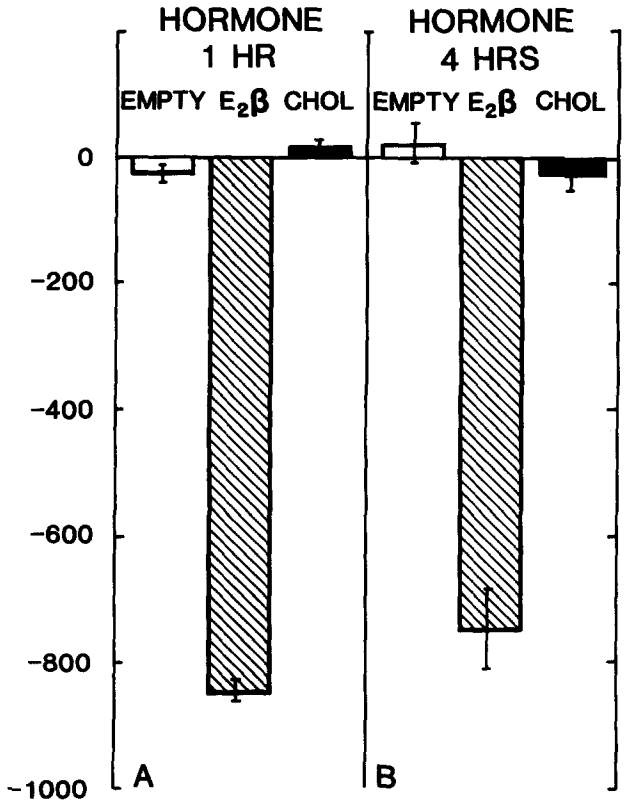

FIG. 3. Behavioral effect of systemically administered APO after intracerebral application of a steroid. The intracerebral application of a steroid was made by inserting an estrogen-filled ($E_2\beta$), cholesterol-filled (CHOL) or empty (EMPTY) cannula through the guide cannula into the brain tissue on one side of the brain. (3-A) Average difference score in response to APO after application of steroid into the dorsal striatum for 1 hour (n=43). All other details as in Fig. 2-A. (3-B) Average difference score in response to APO after application of steroid into the dorsal striatum for 4 hours (n=43). All other detail as in Fig. 2-A.

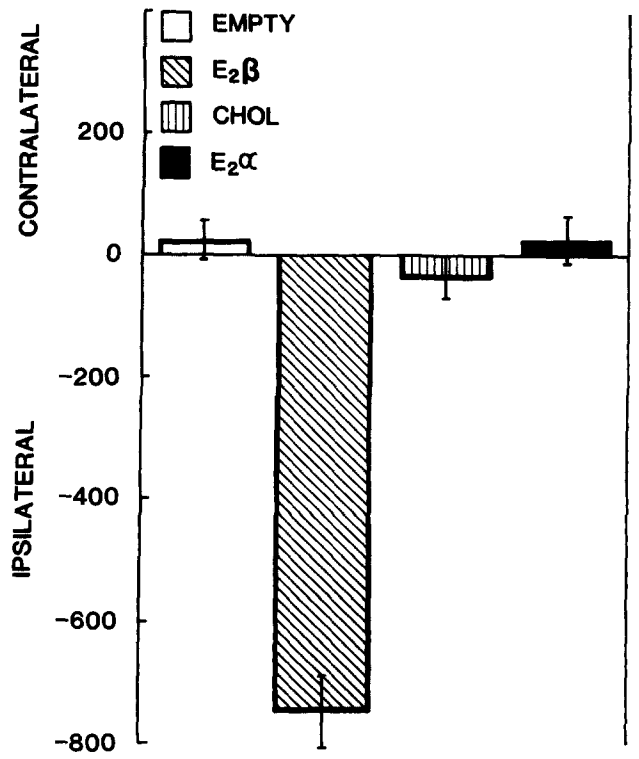

FIG. 4. Behavioral effect of systemically administered APO after intrastriatal application of a steroid. The intracerebral application of a steroid was made by inserting an estrogen-filled ($E_2\beta$), cholesterol-filled (CHOL), 17α-estradiol-filled ($E_2\alpha$) or empty (EMPTY) cannula through the guide cannula into the brain tissue on one side of the brain (n=17 for each). Average difference score in response to APO after application of steroid into the dorsal striatum. All other details as in Fig. 2-A.

EXPERIMENT 2

The results of Experiment 1 suggest that the insertion of estradiol into the dorsal striatum antagonizes one effect of APO in that striatal region, as measured by the ipsilateral asymmetry of the stereotypic behaviors. This region of the striatum is sensitive to DA-induced contralateral postural deviation, an asymmetry of the animal's behaviors [11]. To test the specificity of this effect of estradiol, a comparison was made between estradiol, 17α-estradiol and cholesterol.

Procedure

OVX rats (n=17) were given unilateral inserts of estradiol, 17α-estradiol, cholesterol, and an empty cannula into the dorsal striatum on separate days. After the insertion, the rats were returned to their home cages for 4 hours; then the insert cannula was removed and the rats were injected with APO (0.70 mg/kg, IP) for testing.

Statistical Analyses

In order to obtain an index of the dominant direction of postural deviation the time spent ipsilateral was subtracted from the time spent contralateral to the side of the intracerebral insertion of the steroid (difference score). The difference scores for the total 20 min of the observation period were analyzed for differences due to the steroid implanted (HORMONE), using within-subjects comparisons. An analysis of covariance was used to determine if the variable HORMONE (4 levels) had a significant overall effect. Tests for simple main effects were then made using Scheffé's method for multiple comparisons (equal sample size).

RESULTS

The specific stereotypic behavioral syndrome induced by APO was not altered by the insertion of any steroid into the dorsal striatum. However, as observed previously in these same animals (Experiment 1), insertion of estradiol into the dorsal striatum produced ipsilateral directing of the stereotypic behaviors, as indicated by the large difference score (Fig. 4, $p<0.01$). Inserts of 17α-estradiol and cholesterol were no more effective than an empty cannula insert (Fig. 4), in that APO-induced stereotypies were directed both ipsilaterally and contralaterally to the side of the intrastriatal insert of the steroids and small difference scores were obtained. Rats used in this experiment were subse-

quently found to have had cannula placements within the dorsal striatum.

EXPERIMENT 3

The results of Experiment 2 indicate that the antagonism of one dorsal striatal effect of APO by estradiol has some specificity. Other steroids tested, cholesterol and 17α-estradiol, were not effective in producing ipsilateral directing of the APO-induced stereotypic behaviors. To test if an ipsilateral intrastriatal insertion of estradiol produced a nonspecific depression of all neuronal activity in that region, different doses of APO were administered.

Procedure

OVX rats (n=12) were given unilateral inserts of estradiol and an empty cannula into the dorsal striatum on separate days. After insertion the rats were returned to their home cages for 4 hours; then the insert cannula was removed and the rats were injected with 3 different doses of APO, on separate days, for testing. The administration of the three doses of APO was counterbalanced. The doses were 0.07 mg/kg; 0.75 mg/kg; and 3.0 mg/kg.

Statistical Analyses

In order to obtain an index of the dominant direction of postural deviation the time spent ipsilateral was subtracted from the time spent contralateral to the side of the intracerebral insert of the steroid (difference score). The total 20 min of the observation period were analyzed for differences due to the dose of APO (DRUG), using within-subjects comparisons. An analysis of covariance was used to determine if the variable DRUG (3 levels) had a significant overall effect. Tests for simple main effects were then made using Scheffé's method for multiple comparisons (equal sample size).

RESULTS

Each dose of APO produced a reliable stereotypic behavioral syndrome. As has been found previously with unoperated rats [3], the 3.0 mg/kg dose produced stereotypic gnawing and licking; the 0.75 mg/kg dose produced stereotypic sniffing and locomotion; and the 0.07 mg/kg dose produced an inhibition of all active behaviors. Insertion of estradiol or an empty cannula into the dorsal striatum did not alter the characteristics of each APO-induced behavior pattern.

As was observed previously (Experiment 1), rats given an insertion of estradiol into the striatum showed ipsilateral directing of the stereotypic behaviors to a 0.75 mg/kg dose of APO (Fig. 5). When given a dose of 0.07 mg/kg APO, there was a greater difference score than with the 0.75 mg/kg dose (Fig. 5, $p<0.01$), indicating that the rats were deviated ipsilaterally for a greater proportion of the observation time. When given a dose of 3.0 mg/kg APO there was no significant difference score for postural deviation (Fig. 5). Rats used in this experiment were subsequently found to have had cannula placements in the dorsal striatum.

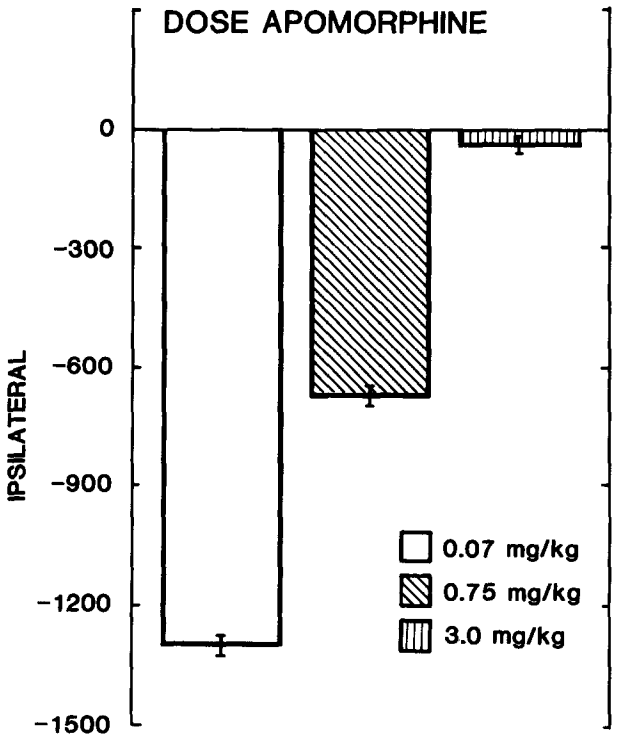

FIG. 5. Behavioral effect of three different doses of systemically administered APO after intrastriatal application of a steroid (n=12 for each). The intracerebral application of a steroid was made by inserting an estrogen-filled ($E_2\beta$) or empty (EMPTY) cannula through the guide cannula into the brain tissue on one side of the brain. Average difference score in response to APO after application of steroid into the dorsal striatum. All other details as in Fig. 2-A.

GENERAL DISCUSSION

The technique of insertion of estrogen into specific regions of the brain has proven useful in identifying the site of its action in neuroendocrine events and sexual behavior. For example, insertion of very small amounts of estradiol into the ventromedial hypothalamus can induce sexual receptivity in OVX rats (e.g., [5]). In the present series of experiments this technique was applied to the study of estradiol's actions in the dorsal striatum. This study demonstrates that estradiol can exert a regionally- and structurally-specific suppression of a striatal APO effect, and that this suppression is relatively rapid.

Asymmetry of the active behaviors of a rat can be produced by altering the balance of dopaminergic activity between the two striata (see [9]). Intrastriatal DA-induced contralateral asymmetry of behaviors, or postural deviation, can be elicited by application of DA to a circumscribed region of the anterior dorsal striatum [10]. If estradiol directly suppresses the postsynaptic effects of APO, a DA agonist, then an insert of estradiol into this circumscribed region should produce an ipsilateral asymmetry of the stereotypic behaviors induced by APO given systemically. The results of Experiment 1 indicated that an insert of estradiol into the dorsal striatum, but not into sites immediately surrounding this region, were effective in producing the ipsilateral asymmetry. It is our hypothesis that this indicates an antagonism of one striatal effect of APO. The effect was apparent as early as 1 hour after insertion of estradiol into the dorsal striatum. The size of the region within which an insertion of estradiol can alter DA-sensitive postural deviation appears to be quite limited. Inserts of estradiol 0.5 mm ventral or dorsal to the effective region eliminated the capacity of estradiol in suppressing APO. The site of estradiol's effects on postural deviation appears to be more restricted than the

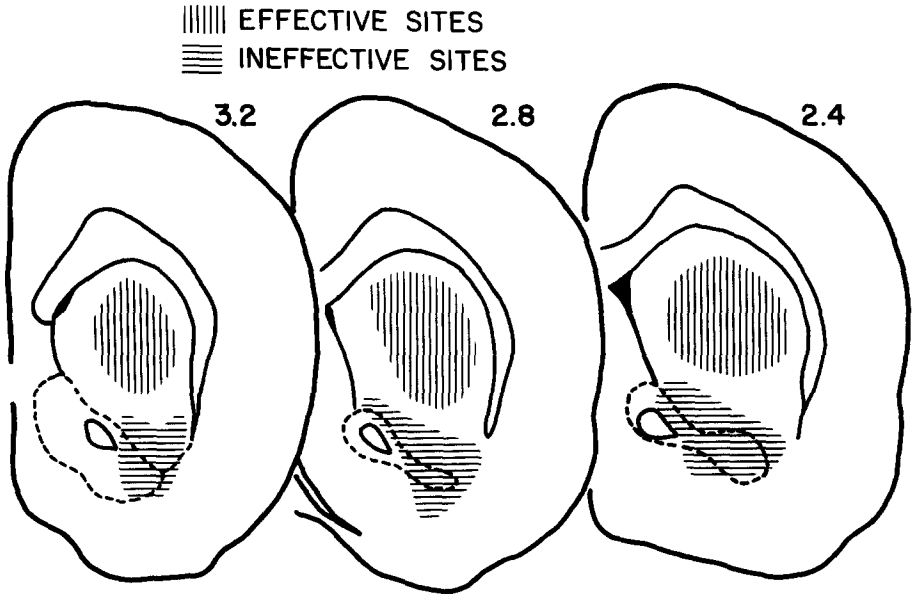

FIG. 6. Effective and ineffective sites for intrastriatal DA-induced postural deviation. Diagram derived from Pellegrino *et al.* [23]. Vertical lines indicate region (dorsal striatum) in which injections of DA (25 μg/0.25 μl) produces contralateral postural deviation. Horizontal lines indicate region (ventral striatum) in which injections of DA do not produce postural deviation. Data from [11,12]; n=200.

region that is sensitive to intrastriatal injections of DA; compare Fig. 1. with Fig. 6. This strongly suggests that estrogen can act directly in the dorsal striatum to suppress a DA-mediated effect, and thus produce postural deviation.

The results of previous studies [12] have suggested that estrogen's suppression of contralateral postural deviation induced by intrastriatal injection of DA might occur through a direct interaction with putative estrogen membrane receptors in the striatum. The possibility that estrogen can interact with putative membrane receptors in other regions of the brain [26] has been based, in part, on the evidence that extracellular iontophoresis of estradiol onto neurons in the anterior hypothalamus produces rapid changes in electrical activity of the neurons [13–17, 24]. The possibility that estradiol was acting at a specific receptor was supported, in part, by the evidence that the inactive isomer of estradiol, 17α-estradiol, was ineffective in producing changes. Other authors have proposed that estradiol can also act in the striatum through membrane receptors to antagonize the electrophysiological responses to iontophoretically applied DA [1]. The studies reported here extend the findings of that electrophysiological research, showing that intrastriatal application of 17β-estradiol can modify one striatal DA-mediated behavioral effect. The structural specificity of this estrogen effect was shown in Experiment 2 by comparing the effectiveness of estradiol with two other steroids, cholesterol and 17α-estradiol. The postysynaptic effects of APO in the striatum were suppressed only with implantation of estradiol; cholesterol and 17α-estradiol were ineffective. This selectivity for the 17β as compared to the 17α-enantiomer of estradiol is consistent with a potential interaction with a specific receptor in the striatum.

The possibility that the application of estradiol into one striatum produces a "nonspecific" suppression of that striatum was addressed in Experiment 3. At the 3.0 mg/kg dose of APO an implant of APO did not produce an asymmetry of the stereotypic behavior. It is our supposition that this indicates that the inhibitory effect of the estradiol applied to the dorsal striatum was completely overcome with the highest dose of APO used. This would indicate that the implant of estradiol was not producing a nonspecific suppression of neural activity in the striatum. Alternately, however, the 3.0 mg/kg dose of APO may produce a stereotypic behavior, that of gnawing, that is nonlateralized. Consequently, an insert of estradiol into the dorsal striatum might not produce an asymmetry of the behavior at that dose of APO. It appears, however, that it is not the behavior itself, but the dose, that is important. Manipulations of dopaminergic activity in one striatum induce a lateralization of APO-induced gnawing when the dose of APO is less than 3.0 mg/kg [11]. Therefore, it is reasonable to assume that APO was acting in the dorsal striatum at high enough levels to overcome the effect of estradiol.

Interestingly, it was shown in Experiment 3 that various doses of APO produced specific classes of stereotypic behaviors that were not altered by estradiol application to the striatum. Since it has been shown that systemic administration of estrogen suppresses APO-induced stereotypic behaviors [6,22], it was possible that striatal insertions of estradiol would alter the behavioral response to systemically administered APO. However, stereotypic behaviors induced by systemically administered APO probably involve APO's actions in several forebrain regions [4,9]; consequently, it is not surprising that the application of estradiol to a limited region of the striatum does not alter these behaviors. The fact that estrogen could suppress one of the behavioral actions of APO in the striatum suggests that estrogen can act postsynaptically on DA-sensitive neurons in the striatum to antagonize some DA-mediated behaviors. Thus, in the present experiments as in previous work [6,22], the short-term effect of estrogen is suppression of some striatal DA-mediated behaviors.

ACKNOWLEDGEMENTS

The research reported here was supported by a Biomedical Research Grant awarded to Dr. C. Van Hartesveldt. Our appreciation is extended to Drs. N. Rowland and W. G. Luttge for their helpful comments on initial versions of this manuscript.

REFERENCES

1. Arnauld, E., B. Dufy, M. Pestre and J. D. Vincent. Effects of estrogens on the responses of caudate neurons to microiontophoretically applied dopamine. *Neurosci Lett* **21:** 325–331, 1981.
2. Costall, B., C. X. DeSouza and R. J. Naylor. Topographical analysis of the actions of 2-(N,N-dipropyl) amino-5,6-dihydroxytetralin to cause biting behaviour and locomotor hyperactivity from the striatum of the guinea pig. *Neuropharmacology* **19:** 623–631, 1980.
3. Costall, B. and R. J. Naylor. The role of telencephalic dopaminergic systems in the mediation of apomorphine-stereotyped behaviour. *Eur J Pharmacol* **24:** 8–24, 1973.
4. Costall, B., R. J. Naylor and R. T. Owen. Investigations into the nature of the peri-oral movements induced by 2-(N,N-dipropyl) amino-5,6-dihydroxytetralin. *Eur J Pharmacol* **45:** 357–367, 1977.
5. Davis, P. G., B. S. McEwen and D. W. Pfaff. Localized behavioral effects of tritiated estradiol implants in the ventromedial hypothalamus of female rats. *Endocrinology* **104:** 898–903, 1979.
6. Gordon, J. H. Modulation of apomorphine-induced stereotypy by estrogen: Time course and dose response. *Brain Res Bull* **5:** 679–682, 1980.
7. Hall, N. R. and W. G. Luttge. Intracerebral progesterone: effects on sexual behavior in female mice. *Society for Neuroscience Meetings*, Abstract No. 240, 1974.
8. Heritage, A. S., W. E. Stumpf, M. Sar and L. D. Grant. Brainstem catecholamine neurons are target sites for sex steroid hormones. *Science* **207:** 1377–1379, 1980.
9. Joyce, J. N. Multiple dopamine receptors and behavior. *Neurosci Biobehav Rev* **7:** 227–256, 1983.
10. Joyce, J. N., R. E Davis and C. Van Hartesveldt. Behavioral effects of unilateral dopamine injection into dorsal or ventral striatum. *Eur J Pharmacol* **72:** 1–10, 1981.
11. Joyce, J. N., R. E. Davis and C. Van Hartesveldt. Systemic apomorphine reverses intrastriatal dopamine-induced contralateral deviation. *Eur J Pharmacol* **87:** 283–289, 1983.
12. Joyce, J. N., R. L. Smith and C. Van Hartesveldt. Estradiol suppresses then enhances intracaudate dopamine-induced contralateral deviation. *Eur J Pharmacol* **81:** 117–122, 1982.
13. Kelly, M. J., U. Kuhnt and W. Wuttke. Hyperpolarization of hypothalamic parvocellular neurons by 17B-estradiol and their identification through intracellular staining with procion yellow. *Exp Brain Res* **40:** 440–447, 1980.
14. Kelly, M. J., R. L. Moss and C. A. Dudley. Differential sensitivity of preoptic-septal neurons to microelectrophoresed estrogen during the estrous cycle. *Brain Res* **114:** 152–157, 1976.
15. Kelly, M. J., R. L. Moss and C. A Dudley. The effects of microelectrophoretically applied estrogen, cortisol and acetylcholine on medial preoptic-septal unit activity throughout the estrous cycle of the female rat. *Exp Brain Res* **30:** 53–64, 1977.
16. Kelly, M. J., R. L. Moss and C. A. Dudley. The effects of ovariectomy on the responsiveness of preoptic-septal neurons to microelectrophoresed estrogen. *Neuroendocrinology* **25:** 204–211, 1978.
17. Kelly, M. J., R. L. Moss, C. A. Dudley and C. P. Fawcett. The specificity of the response of preoptic-septal area neurons to estrogen: 17α-estradiol versus 17B-estradiol and the response of extrahypothalamic neurons. *Exp Brain Res* **30:** 43–52, 1977.
18. Luttge, W. G. Cerebral effects of gonadal steroid hormones. In: *Molecular and Behavioral Neuroendocrinology*, edited by A. J. Dunn. New York: Spectrum Publications, in press.
19. Luttge, W. G. and J. R. Hughes. Intracerebral implantation of progesterone: Re-examination of the brain sites responsible for facilitation of sexual receptivity in estrogen-primed ovariectomized rats. *Physiol Behav* **17:** 771–775, 1976.
20. McEwen, B. S. Steroid hormone interactions with the brain: Cellular and molecular aspects. *Rev Neurosci* **4:** 1–30, 1979.
21. McEwen, B. S., A. Biegon, P. G. Davis, L. C. Krey, V. N. Luine, M. Y. McGinnis, C. M. Paden, B. Parsons and T. C. Rainbow. Steroid hormones: Humoral signals which alter brain cell properties and functions. *Recent Prog Horm Res* **38:** 41–92, 1982.
22. Naik, S. R., M. R. Kelkar and U. K. Sheth. Attenuation of stereotyped behaviour by sex steroids. *Psychopharmacology (Berlin)* **57:** 211–214, 1978.
23. Pellegrino, L. J., A. S. Pellegrino and A. J. Cushman. *A Stereotaxic Atlas of the Rat Brain*. New York:Plenum Press, 1979.
24. Poulian, P. and B. Carette. Pressure ejection of drugs on single neurons in vivo: Technical considerations and application to the study of estradiol effects. *Brain Res Bull* **7:** 33–40, 1981.
25. Stumpf, W. E. and M. Sar. Steroid hormone target sites in the brain: the differential distribution of estrogen, progestin, androgen and glucocorticosteroid. *J Steroid Biochem* **7:** 1163–1170, 1976.
26. Towle, A. C. and P. Y. Sze. Steroid binding to synaptic plasma membrane: differential binding of glucocorticoids and gonadal steroids. *J Steroid Biochem* **18:** 135–143, 1983.
27. Warembourg, M. Radiographic study of the rat brain, uterus and vagina after [3H]R-5020 injection. *Mol Cell Endocrinol* **12:** 67–79, 1978.