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Sex differences in the rapid and acute effects of estrogen on striatal D_2 dopamine receptor binding

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Abstract

Regional changes in striatal D_2 dopamine (DA) receptor binding in castrated (CAST) or ovariectomized (OVX) rats were investigated following administration of a low dose of estradiol benzoate (EB), repeated treatment with EB followed by progesterone, or vehicle. In two separate experiments, there was a significant decrease in striatal D_2 DA receptor binding in caudal striatum from OVX, but not CAST rats 30 min after a single injection of EB. In CAST rats, there was a significant increase in striatal D_2 DA receptor binding in rostral striatum 4 h after injection of EB. There was no effect of EB plus progesterone treatment in either OVX or CAST rats. In addition, CAST rats had significantly lower D_2 DA receptor binding in the lateral region of the rostral striatum than did OVX rats. These results show sexually dimorphic and regionally specific effects of estrogen on striatal D_2 DA receptor binding, and a significant sex difference in striatal D_2 DA receptor binding in the absence of circulating gonadal hormones. The present findings are discussed in light of previous reports of sex differences in gonadal hormone influences on striatal DA mediated behaviors.

Key words: Estradiol; Dopamine receptor; Sex differences; Striatum; Quantitative autoradiography; Progesterone

1. Introduction

Gonadal steroid hormones have been shown to affect D_2 dopamine (DA) receptor binding in rat striatum [4,5,7,9,10,11,14,16,18,20,23,27,28,35]. Of the gonadal steroid hormones, estrogen has received the most attention in this regard. Although there have been apparent discrepancies in the results, an analysis of the differences among the protocols across research groups reveals some consistent effects of estrogen on striatal D_2 DA receptor binding.

The effect of estrogen on striatal D_2 DA receptor binding varies with the dose of estrogen, the sex of the animal, the duration of estrogen treatment, and the period of time after estrogen treatment when receptor binding was measured. For example, two laboratories have reported increased striatal D_2 DA receptor binding following repeated administration of high doses of estrogen. Di Paolo et al. [6,7,9] found that 20 μg/day 17β-estradiol for 14 days increased the B_{max} for striatal D_2 DA receptors in ovariectomized (OVX) female rats 24 h after the last estradiol injection. Other methods used to chronically elevate circulating estrogen levels have produced similar results. For example, in intact female rats there was a significant increase in the B_{max} for striatal D_2 DA receptors after one month exposure to subcutaneous pellets containing 10 mg estradiol benzoate (EB) [14]. Chronic elevation of circulating estrogen following a single injection of the long acting estradiol valerate also increased the B_{max} for striatal D_2 DA receptors in both intact male and OVX rats [18,20,23].

Taken together, the studies discussed above suggest that chronic elevation of circulating estrogen increases striatal D_2 DA receptor binding. In each of the above experiments, however, the dose of estrogen used to produce effects was considerably higher than that required to approximate circulating estrogen concentrations in an intact female rat. Thus, there are inherent difficulties in relating findings from studies using

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chronic high doses of estrogen, to results of studies that examine changes in striatal D_2 DA receptor binding that occur in response to brief changes in physiological concentrations of circulating estrogen, such as those that occur during the four day estrous cycle.

Work by Gordon and colleagues [5,16] has shown that the effect of estrogen on striatal DA receptor binding can vary with the time after hormone treatment. These investigators treated OVX rats with 25 μg EB/day for 3 days and found that there was decreased affinity for DA receptor binding 24 h after the last injection [4,16]. By contrast, 48–96 h after the final EB injection the B_{max} for striatal D_2 DA receptors was increased [5,16]. Thus, even with a relatively high dose of estrogen, when the duration of the treatment period more closely approximates the period of the estrous cycle the effect of estrogen is different from that seen with more chronic treatment.

Studies that have investigated changes in striatal D_2 DA receptor binding in response to low doses of estrogen or estrous cycle dependent changes in circulating estrogen have also consistently found effects that are quite different from the response to chronic high dose treatment. For example, the ratio of high/low affinity states of striatal D_2 DA receptors is greater during diestrus, when circulating estrogen is low than during proestrus when circulating estrogen levels are rapidly rising [8]. Using a dose of EB that approximates the endogenous serum concentrations of estrogen, Tonnaer and colleagues [35] found that 2.5 μg EB/day for 7 days decreased the affinity of striatal D_2 DA receptors 24 h after the final EB injection in OVX rats. Similarly, Levesque and DiPaolo [27] found that administration of a single low dose (100 ng) of 17β-estradiol to OVX rats also resulted in conversion of high affinity D_2 DA binding sites to low affinity binding sites 30 min after injection. Reducing circulating estrogen by ovariectomy, on the other hand, significantly increased the ratio of high/low affinity state of striatal D_2 DA receptors [27]. To date, an effect of an acute physiological dose of estrogen on striatal D_2 DA receptor binding in male rats has not been reported.

The studies discussed above have all used homogenates of striatal tissue to determine whether estrogen affects striatal D_2 DA receptor binding. However, the striatum is structurally and functionally heterogeneous. As described by Gerfen ([13], p. 19), "the dorsal region of the striatum receives inputs from sensorimotor cortical areas (among other areas) and projects to the substantia nigra pars reticulata, whereas the ventral striatum receives inputs from limbic brain areas such as the olfactory cortex, amygdala and hippocampus and projects to the substantia nigra pars compacta". In addition, there is compartmentation within the striatum, referred to as the patch/matrix organization [13]. Superimposed on this already complex organization of the striatum, there is a lateral to medial gradient in the binding density of D_2 DA receptors [25]. In the only studies reporting regional effects of systemically administered estradiol on striatal DA receptors, 20 μg/day EB for 14 days increased the number of striatal D_2 DA receptors selectively in the lateral portion of the striatum in OVX rats 24 h after the last EB injection [12,26]. Thus, the effects of estrogen on striatal D_2 DA receptor binding may be regionally specific.

The present studies were designed to further delineate the regional specificity of striatal D_2 DA receptor binding changes that respond to physiological concentrations of gonadal steroid hormones. Regional effects were examined following administration of an acute low dose of estrogen to gonadectomized male and female rats. In addition, the effect of a hormone administration regimen designed to approximate the rat's estrous cycle was examined in both male and female gonadectomized rats.

2. Materials and Methods

2.1 Subjects

Adult male and female Holtzman rats (Harlan Sprague–Dawley Inc., Indianapolis, IN) were gonadectomized under ether anesthesia in accordance with guidelines set by the University Committee on Use and Care of Animals. All animals were allowed 14 days to recover from surgery. During that time cells from the vaginal epithelium of OVX rats were examined daily for 10 days, only OVX rats with vaginal epithelial cells showing no evidence of cornified cells were used for the remainder of the experiment.

2.2 General procedures

Horizontal brain sections from a total of 18 castrated (CAST) male and 22 OVX rats were analyzed for the first experiment. Rats were assigned to one of three treatment groups. Estradiol benzoate (EB) and progesterone (Sigma Chemical Co., St. Louis, MO) were dissolved in peanut oil and injected subcutaneously. One group of 6 CAST and 7 OVX rats received 20 μg EB/kg for three days and 4.8 mg progesterone/kg on the fourth day. These doses of EB and progesterone produce serum concentrations within the physiological range [2,17]. Animals from this group were killed by decapitation 4 h after the progesterone injection (EB+P). A second group of 6 CAST and 8 OVX rats received three days of vehicle (peanut oil) injections and a single injection of 20 μg EB/kg on the fourth day. Animals from this group were killed by decapitation 30 min after the EB injection (EB.30). A third group of 6 CAST and 7 OVX rats received four days of vehicle injections. Half of the animals from this group were killed by decapitation 30 min after the final injection, the other half 4 h after injection (OIL).

Coronal brain sections from a total of 23 CAST and 20 OVX rats were analyzed for the second experiment in order to determine if a single injection of EB would produce changes in striatal D_2 DA receptor binding 30 min or 4 h after injection. Rats of each sex were assigned to one of three treatment groups. In the first group, 5 CAST and 6 OVX rats each received 20 μg EB/kg and were killed by decapitation 30 min after the injection (EB·30). In the second

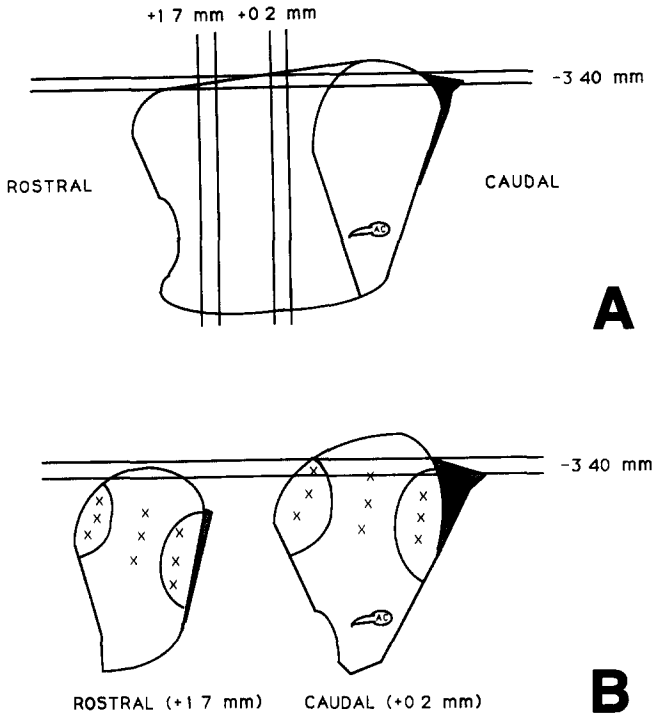

Fig. 1. A schematic diagram illustrating the relative positions of the horizontal and coronal sections taken for this study. A: the left striatum is depicted with lines through the horizontal and coronal planes that were sectioned Values indicated the approximate distance from bregma (skull flat) estimated from Paxinos and Watson [29]. The darkened area at the top right of the striatum is the lateral ventricle. B: schematic drawings of the shapes of the left striatum at the two coronal planes, with the plane of the horizontal sections indicated with the horizontal lines Note that horizontal sections were sampling primarily caudal striatum AC, anterior commisure; LV, lateral ventricle.

treatment group, 7 CAST and 6 OVX rats each received 20 μg EB/kg and were killed by decapitation 4 h after injection (EB:4). In the third treatment group, 11 CAST and 8 OVX rats each received a vehicle injection Half of the animals from the vehicle group were killed by decapitation 30 min after the final injection, the other half 4 h after injection (OIL). Coronal sections were used to allow assessment of both rostral and caudal regions of the striatum, since only caudal regions of the striatum were represented in the horizontal sections obtained in the first experiment (Fig. 1).

For all animals, brains were rapidly removed following decapitation and immediately frozen on dry-ice Brains were then stored at -70°C until being sectioned on a cryostat for autoradiographic assay

2 3 Quantitative dopamine receptor autoradiography

Quantitative receptor autoradiography for striatal D_2 DA receptor binding as indicated by [^{3}H]spiperone binding was conducted using methods described in detail elsewhere [32] In brief, for horizontal sections, five consecutive 20 μm frozen sections were collected using a cryostat at -18°C Sections were cut on a horizontal plane between approximately -3.4 and -3.6 mm from the dorsal surface. For coronal sections, five consecutive 20 μm frozen sections were cut on a coronal plane starting approximately 1 7 mm anterior from bregma (rostral striatum), and 5 sections were similarly collected starting approximately 0.2 mm anterior from bregma (caudal striatum). Plane of section and coordinates for brain sections collected were determined by comparing sections with the illustrations in Paxinos and Watson [31] as they were being cut. Sections were thaw-mounted onto gelatin-coated slides, and stored at -70°C until assayed. The D_2 DA receptor binding assay was conducted using a buffer containing 25 mM Tris-HCl (pH 7 5), 100 mM NaCl, 1 mM $MgCl_2$, 15 μM pargyline and 0.001% ascorbate To determine total D_2 DA receptor binding, brain sections ($n = 3$/animal) were incubated in [^{3}H]spiperone (Amersham) at a concentration equal to K_d (250 pM) for 2 5 h at room temperature 100 nM mianserin (Sigma) was added to the buffer to block [^{3}H]spiperone binding to the 5-HT$_2$ serotonin receptor subtype To determine nonspecific binding, brain sections ($n = 2$/animal) were incubated in [^{3}H]spiperone as above, with the addition of 10 μM dopamine-HCl After incubation with the tritiated ligand, sections were washed for 10 min in buffer at 4°C, dipped in distilled water (4°C), and then dried using a stream of cool air Sections were then apposed to Amersham Hyperfilm-^{3}H, with previously calibrated [^{14}C]methacrylate standards [30] Horizontal sections were apposed to film for 21 days Coronal sections were apposed to film for 16 days Films were developed in Kodak D-19 developer and fixed in Kodak rapid fixer

All binding data were determined directly from film densities Films were analyzed using computer-assisted video densitometry Specific binding for striatal D_2 DA receptor binding was determined by subtracting the average densities of non-specific [^{3}H]spiperone binding from the average total [^{3}H]spiperone binding for each animal

2 4 Regional analysis of the striatum

In horizontal sections, D_2 DA receptor density was quantified in both the lateral and the medial regions of the dorsal striatum (Fig. 2A) In coronal sections, D_2 DA receptor density was quantified in the lateral, central and medial regions of both the rostral and caudal striatum (Fig. 2B)

2.5. Statistics

Data were analyzed by analysis of variance (ANOVA) using Statview 512+ for the Macintosh computer

3. Results

3.1. Horizontal sections

Within the OVX and CAST groups, there were no significant differences in D_2 DA receptor binding between OIL treated animals killed 30 min after injection and those killed 4 h after injection. Therefore, data from animals taken 30 min or 4 h after oil treatment were combined to yield a single OIL injected group for OVX and a single OIL injected group for CAST rats.

Using these comparison groups, there was a significant decrease in striatal D_2 DA receptor binding in OVX rats that were killed 30 min after a single EB injection compared to OIL injected OVX rats ($F_{1,13} = 8.046$; $P = 0.014$; Fig. 3) and to EB + P injected OVX rats ($F_{1,13} = 0.0016$; $P = 0.0016$; Table I). There was a lateral to medial gradient in D_2 DA receptor binding ($P < 0.001$), and the decrease in D_2 DA receptor binding in these dorsal horizontal sections was found in

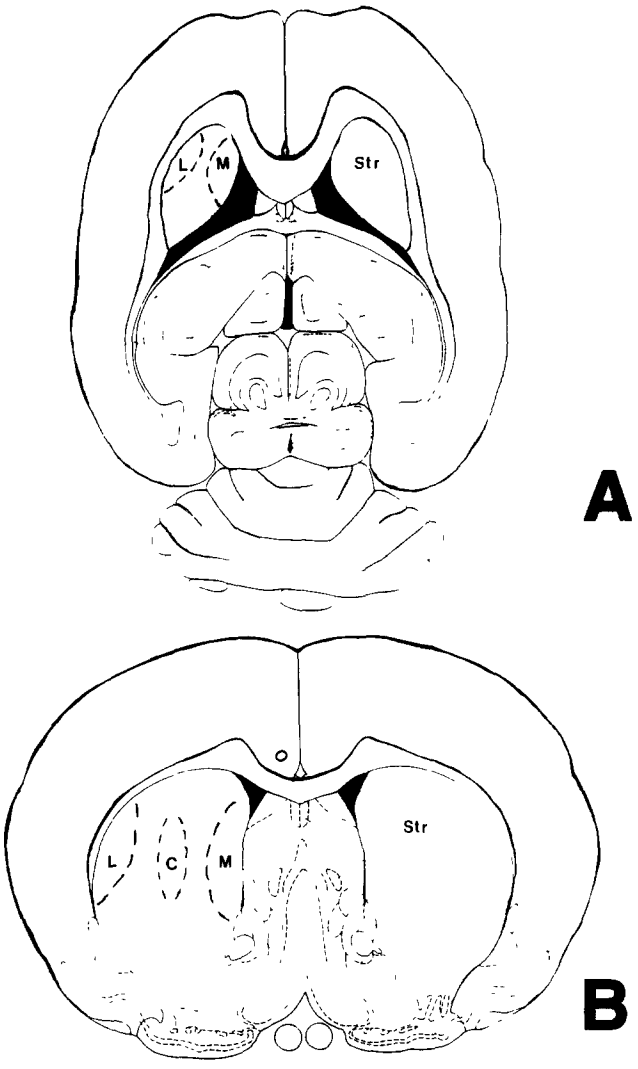

Fig 2. Areas of the striatum sampled for regional analysis of D_2 DA receptor binding density in horizontal (A) and coronal (B) sections through the striatum (Str) are depicted. A· in horizontal sections, approximately −3 6 mm from top of skull at bregma, lateral (L) and medial (M) areas as indicated above were assessed bilaterally B· in coronal sections, approximately +1 7 and +0.2 mm from bregma (skull flat), as indicated above, the lateral (L), central (C), and medial (M) regions of striatum were assessed bilaterally (Figures adapted from Paxinos and Watson [29].)

both lateral and medial regions of the striatum. Receptor binding in OVX rats that received EB + P was not significantly different from OVX rats that received OIL.

In CAST rats, there were no significant differences between the three treatment groups in D_2 DA receptor binding density. In addition, there were no sex differences in D_2 DA receptor binding in horizontal sections (Table 1) which represents the dorsal caudal striatum.

3.2. Coronal sections

As was true for the horizontal sections, there were no significant differences within the OVX and CAST groups in D_2 DA receptor binding between OIL treated animals killed 30 min after injection and those killed 4 h after injection. Therefore, data from coronal sections of animals taken 30 min or 4 h after oil treatment were combined to yield a single OIL injected group for OVX and a single OIL injected group for CAST rats.

Using these comparison groups, there was a significant decrease in D_2 DA receptor binding in the caudal striatum of OVX rats 30 min after a single injection of EB, compared to OVX rats receiving only vehicle (Fig. 3). There was a lateral to medial gradient in the density of D_2 DA receptor binding in all groups ($P < 0.001$) and the decrease in D_2 DA receptor binding was significant in all three regions of the caudal striatum ($F_{1,14} = 6.33$; $P = 0.025$). There was no significant effect of the EB treatment in the rostral striatum of OVX rats, and no effect 30 min after EB treatment on D_2 DA receptor binding in CAST animals (Table II).

By contrast, there was an increase in D_2 DA receptor binding in the rostral striatum of CAST rats 4 h after a single injection of EB, compared to CAST rats receiving only vehicle (Fig. 4). This increase in D_2 DA receptor binding was significant in all three regions of the rostral striatum ($F_{1,16} = 15.16$; $P = 0.0013$), but was not significant in the caudal striatum (Table II). There was no effect 4 h after EB treatment on D_2 DA receptor binding in OVX animals in either region of the striatum.

There was also a sex difference in D_2 DA receptor binding in the rostral striatum of OIL injected rats. OIL injected CAST rats had less D_2 DA receptor binding than OIL injected OVX rats (Fig. 5). Both CAST and OVX rats showed the lateral to medial gradient in D_2 DA receptor binding ($F_{1,2} = 58.48$; $P < 0.001$). The sex difference in D_2 DA receptor binding was significant only in the lateral region of the rostral striatum ($F_{1,19} = 5.973$; $P = 0.0245$), although the trend was evident throughout the lateral to medial gradient (Table II).

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Fig. 3. Autoradiograms from OVX rats in representative horizontal (A–D) and coronal (E–H) sections are shown illustrating total [^{3}H]spiperone binding (A,B,E,F) and non-specific binding (C,D,G,H) after oil treatment (A,C,E,G) or 30 min after 20 μg EB/kg (B,D,F,H). There was a significant decrease in specific D_2 DA receptor binding (total minus blank) 30 min after EB in both horizontal sections ($P = 0.014$) and caudal coronal sections ($P = 0$ 025) compared with oil treated controls A representative calibration bar for D_2 DA receptor binding density is shown on the right of the figure.

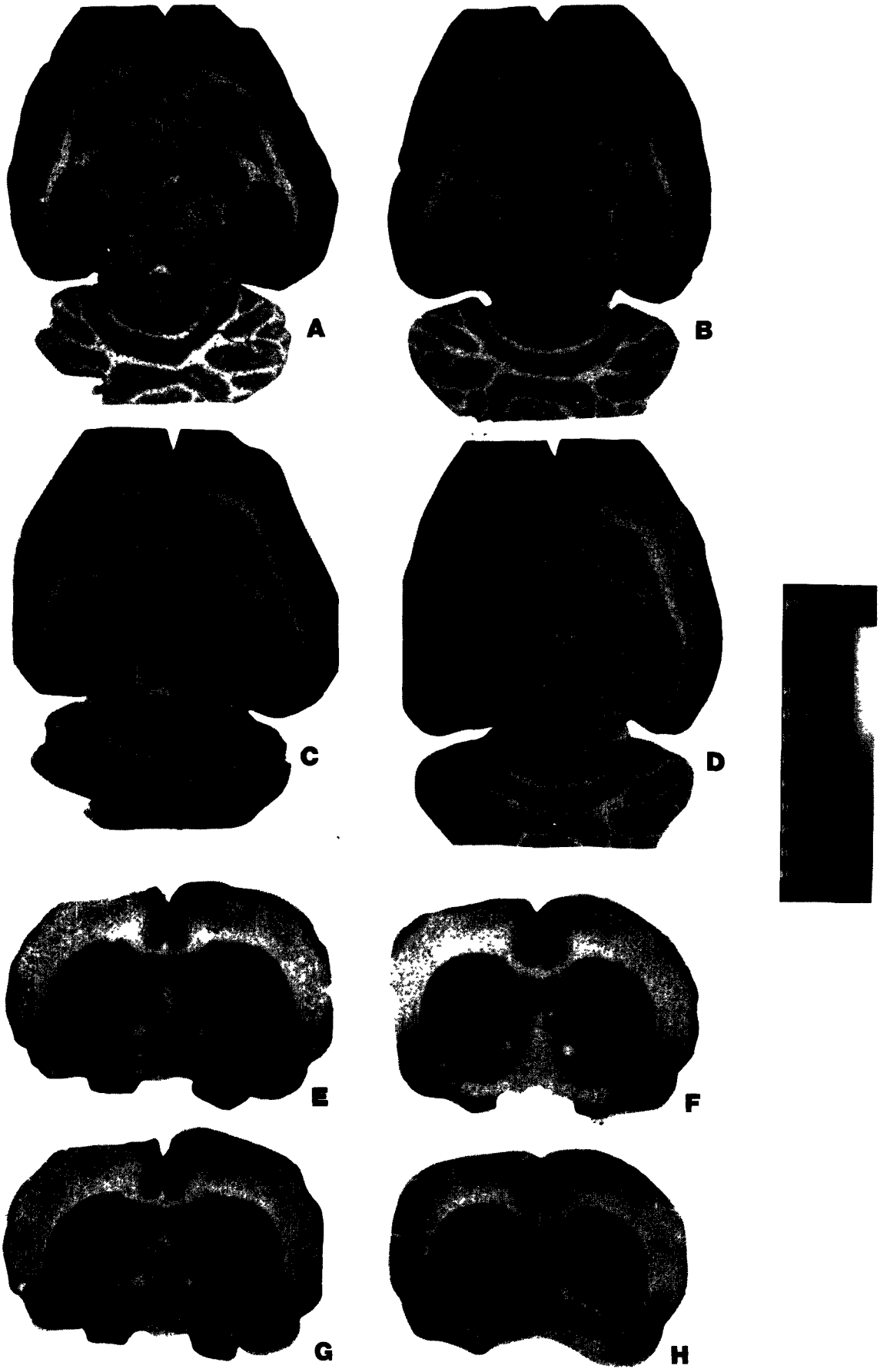
A
B
C
D
E
F
G
H

Table 2
D_2 DA receptor binding [a] in coronal sections

Treatment	Group (n)	Rostral			Caudal		
		Lateral	Central	Medial	Lateral	Central	Medial
OIL	OVX (10)	201 ± 15 [d]	173 ± 16	144 ± 3	175 ± 8	144 ± 5	90 ± 3
	CAST (11)	155 ± 11	145 ± 10	135 ± 8	171 ± 13	136 ± 7	83 ± 4
EB·30	OVX (6)	168 ± 31	154 ± 26	139 ± 19	135 ± 19 [b]	111 ± 13 [b]	72 ± 9 [b]
	CAST (5)	177 ± 27	163 ± 23	158 ± 22	173 ± 21	140 ± 9	81 ± 6
EB 4	OVX (6)	195 ± 33	172 ± 25	154 ± 19	168 ± 21	133 ± 17	77 ± 7
	CAST (7)	236 ± 22 [c]	222 ± 20 [c]	199 ± 16 [c]	179 ± 13	157 ± 18	96 ± 9

[a] pmol/mg protein; mean ± S E M.
[b] $P < 0.05$ vs. oil treated rats of the same sex.
[c] $P < 0.05$ vs. oil treated rats of the same sex
[d] $P < 0.05$ vs male rats from the same treatment group

Since 21 days of film exposure to horizontal sections yielded receptor density counts in the upper third of the standard range, coronal sections were apposed to hyperfilm for 16 days in an effort to avoid a possible ceiling efffect when analyzing films. As anticipated, this reduction in exposure time resulted in lower density readings for coronal sections. D_2 DA receptor binding 30 min after EB was decreased 11–15% in the dorsal caudal horizontal sections and 20–23% in the caudal coronal sections, suggesting that there may have been a partial ceiling effect with the horizontal sections. Nevertheless, this effect of EB was statistically significant in both experiments.

4. Discussion

This is the first report of a sex difference in the effects of EB on striatal D_2 DA receptor binding. Furthermore, there is intrastriatal regional variability in the response to EB and in the time course of the response. In OVX, but not CAST rats, D_2 DA receptor binding in caudal striatum was decreased 30 min after a single injection of EB. In CAST, but not OVX rats, EB treatment resulted in increased D_2 DA receptor binding 4 h later in the rostral striatum. These results demonstrate that the rapid effects of estrogen reported here are both regionally specific and sex-

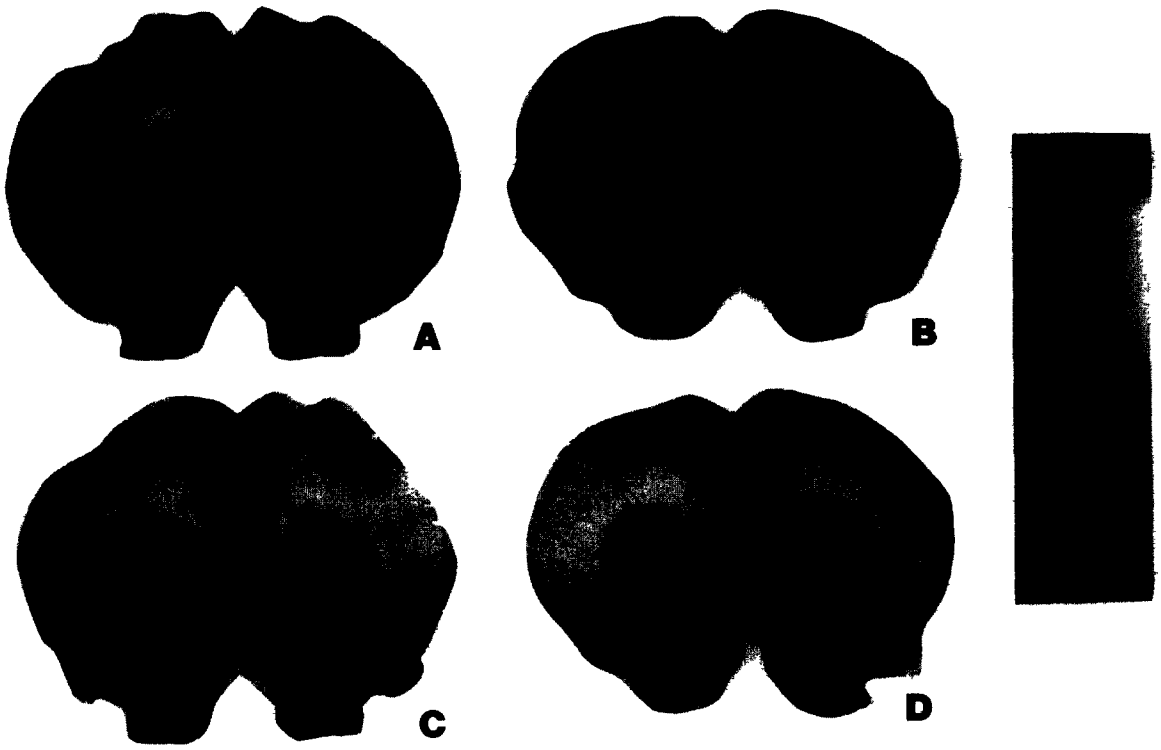

Fig 4. Autoradiograms from CAST rats after oil treatment (A,C) or 4 h after after 20 μg EB/kg (B,D) is shown in representative coronal sections illustrating total [^{3}H]spiperone binding (A,B) and non-specific binding (C,D). Specific D_2 DA receptor binding (total minus blank) in coronal sections from rostral striatum was significantly increased 4 h after EB treatment ($P = 0.0013$) compared with oil treated controls A calibration bar for D_2 DA receptor binding density is shown at the right of the figure

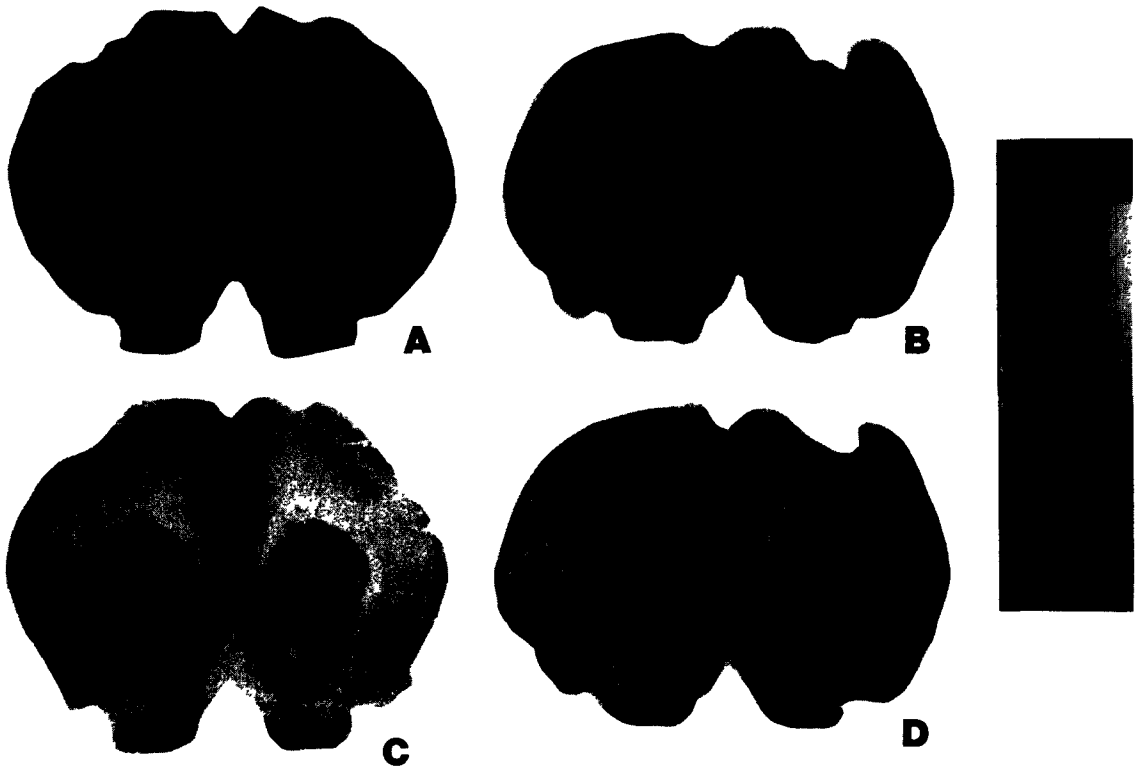

Fig. 5. There were sex differences in specific binding of [^{3}H]spiperone in autoradiograms from CAST (A,C) and OVX (B,D) rats. Representative coronal sections from the rostral striatum show total [^{3}H]spiperone binding (A,B) and non-specific binding (C,D). In the rostral striatum there was a significant difference in specific D_2 DA receptor binding (total minus blank) ($P = 0.0245$) in the absence of gonadal hormones A calibration bar for D_2 DA receptor binding density is shown at the right of the figure.

specific and are not likely to be due to non-specific, generalized effects of estrogen on neuronal membranes. Finally, there was a sex difference in D_2 DA receptor binding in the lateral region of the rostral striatum where the binding density was lower in CAST than in OVX rats.

Previous research has revealed that neuronal receptors can exhibit rapid changes in response to systemic administration of gonadal hormones. For example, 30 min following progesterone injection, oxytocin receptor binding is increased in rat hypothalamus [34]. Rapid changes in DA receptor binding have also been reported following estrogen injection. Levesque and DiPaolo [27] reported a decrease in the ratio of high/low affinity striatal D_2 DA binding sites in OVX rats 30 min after a single low dose of 17β-estradiol. The results of Levesque and DiPaolo [27] are in close agreement with the present finding of a rapid decrease in striatal D_2 DA receptor binding following an acute injection of EB. The present report, however, has extended this finding by showing the response to be sexually dimorphic, occurring in OVX but not CAST rats.

Table 1
D_2 DA receptor binding [a] in horizontal sections

Treatment	Group (n)	Medial striatum	Lateral striatum
OIL	OVX (7)	286 ± 10	399 ± 14
	CAST (6)	287 ± 17	386 ± 27
EB·30	OVX (8)	247 ± 5 [b]	358 ± 16 [b]
	CAST (6)	264 ± 23	389 ± 28
EB+P 4	OVX (7)	274 ± 11	429 ± 9
	CAST (6)	277 ± 27	386 ± 28

[a] pmol/mg protein; mean ± S.E.M
[b] $P < 0.04$ less than OIL or EB+P treated females, see text for additional details.

The finding of a lateral to medial gradient in striatal D_2 DA receptor binding is in agreement with previous work showing a similar gradient in both D_2 DA receptor binding [25] and in D_2 DA receptor mRNA [26]. Although this lateral to medial distribution of receptors seems well established, few previous studies have assessed regional changes in striatal D_2 DA receptor binding in response to estrogen treatment. In those studies that have undertaken regional analysis, the effect of estrogen on striatal D_2 DA receptor binding was reported to be greatest in the lateral region of the striatum. For example, chronic EB treatment was found to increase striatal D_2 DA receptor binding in lateral, but not the medial striatum [12,26]. Crystalline estradiol diluted with cholesterol and introduced directly

into the striatum also produced an increase in D_2 DA receptor binding in the lateral, but not the medial striatum [33]. Recently Morissette et al. [29] have reported rostral caudal differences in the effects of estradiol on degradation and production rate constants of striatal D_2 DA receptors following irreversible blockade. Specifically, estradiol treatment decreased these parameters in the caudal, but not the rostral region of the striatum in OVX rats. In the present report, the decrease in striatal D_2 DA receptor binding 30 min after EB was also restricted to the caudal region of the striatum of OVX rats. No effect was found in CAST rats 30 min after EB. Furthermore, this decrease in D_2 DA receptor binding 30 min after EB was seen in both coronal sections from caudal striatum and in horizontal sections representing dorsal caudal striatum (Fig. 1).

In the present report, the sex difference in D_2 DA receptor binding seen in coronal sections was found to be localized specifically to the lateral rostral striatum, with no sex difference seen in any subregion of the caudal striatum. Since horizontal sections in this report represent primarily the dorsal-caudal region of the striatum (Fig. 1), it is not surprising that a sex difference was not found in sections cut in the horizontal plane.

The report here of a sex difference in the effect of EB on striatal D_2 DA receptor binding may be related to results from previous reports of the effects of estrogen on stimulated striatal DA release [1,3]. For example, when compared to oil injected controls, amphetamine-stimulated striatal DA release in OVX rats was enhanced 30 min after estrogen injection using the same dose of EB (20 μg/kg) as in the present report [1,3]. Conversely, CAST rats, do not show an EB-induced enhancement of amphetamine-stimulated striatal DA release [3], and striatal D_2 DA receptor binding is not changed 30 minutes after EB injection (present report). It is possible, therefore, that the rapid decrease in striatal D_2 DA receptor binding in OVX rats following EB treatment ([27]; present report) is a compensatory response triggered by the EB-induced enhancement of striatal DA release seen in OVX rats [1,3]. It should be noted, however, that the effect of EB on amphetamine-stimulated striatal DA release may also indicate a compensatory response, and that the primary effect of EB may be on striatal D_2 DA receptor binding. Further investigation of the mechanisms mediating these responses may clarify the sequence of events that occur following EB administration in OVX rats.

In the present study, CAST rats showed an increase in striatal D_2 DA receptor binding 4 h after EB injection. Previous research has also found that 24–48 h after repeated or high dose estrogen treatment, there is an increase in striatal D_2 DA receptor binding in both OVX and intact male rats [5,6,7,9,12,14,16,18, 20,22]. In male rats this effect may be mediated by estrogen-induced prolactin release, since after estrogen administration the increase in striatal D_2 DA receptor binding in male rats has been related to circulating serum concentrations of prolactin [19,21,22]. In addition, hypophysectomized male rats that show no prolactin release after estrogen injection show no change in striatal D_2 DA receptor binding, whereas, similarly hypophysectomized female rats do show a significant estrogen induced increase in striatal D_2 DA receptor binding [7,10]. Considering these previous findings, the present results showing a delayed (4 h) increase in striatal D_2 DA receptor binding in CAST rats but not OVX rats may represent a sex-specific response to the secondary effects of estrogen, possibly mediated by prolactin. However, without directly correlating changes in receptor binding with circulating prolactin concentrations, this hypothesis remains speculative.

The present study also revealed a sex difference in striatal D_2 DA receptor binding in the lateral region of the rostral striatum, with CAST rats having significantly less binding than OVX rats. Binding studies using membranes from whole homogenized striatum have found that D_2 DA receptor binding is not significantly different when intact male and female rats are compared [20]. There have been no previous reports comparing striatal D_2 DA receptor binding in CAST rats and OVX rats. Since in vivo microdialysis studies of basal extracellular striatal DA have found higher concentrations of DA in CAST rats compared to OVX rats [3], the sex difference in striatal D_2 DA receptor binding may represent a postsynaptic response to greater striatal DA concentrations in CAST rats relative to OVX rats. Experiments in progress will further investigate this sex difference.

Little is known about the regional differences in striatal function. Although a topographical organization related to cortical regions has been suggested, there is considerable overlap in innervation of the striatum [13]. Data from the current study and previous work [12,33] suggest that D_2 DA receptor binding in the lateral region of the caudal striatum is more sensitive to estrogen than other areas of the striatum, but only in female rats. Furthermore, the present study has revealed that this area of the striatum responds rapidly to EB (within 30 min) with a decrease in D_2 DA receptor binding. Previous research from this laboratory has demonstrated that amphetamine-induced stereotyped head and forelimb movements as well as amphetamine-induce general activity are enhanced 30 min after a single injection of estrogen in OVX rats [3]. Following repeated estrogen treatment in OVX rats, apomorphine-induced stereotyped behavior is more intense than the response seen in control animals [15], and the oral component of apomorphine-induced stereotypy seems to be most sensitive to repeated es-

trogen treatment [24]. Taken together, these findings suggest that the D_2 DA receptor response in the estrogen-sensitive regions of the striatum is particularly important for stereotyped movements of the mouth, head and forelimbs. Additional studies looking at sex differences and/or hormonal influences on spontaneously generated striatal-mediated behaviors are necessary to take full advantage of this paradigm. This brief discussion illustrates, however, the potential value of studying sex differences or hormone influences on striatal mediated behaviors to help elucidate the regional specificity of striatal function.

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