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Inhibition of striatal dopamine transporter activity by 17β-estradiol

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Abstract

Striatal synaptosomes from ovariectomized rats were prepared to examine the effect of 17β-estradiol on [^{3}H]dopamine uptake. Estradiol inhibited [^{3}H]dopamine uptake in a dose-dependent manner, with an IC_{50} of 7.2 μM. Use of identical concentrations of progesterone had no effect on [^{3}H]dopamine uptake. The effects of estradiol were exerted by decreasing the affinity of the transporter for dopamine, as revealed by a dose-dependent increase in the K_m. The K_m values for 0 (control), 10, and 100 μM estradiol were 108 ± 11, 258 ± 44 and 415 ± 40 nM, respectively, with each of the three concentrations tested being significantly different among each other. No statistically significant differences were obtained for the V_{max}, with values for the three increasing doses being 9.2 ± 0.8, 8.3 ± 0.5 and 7.3 ± 0.8 pmol/min per mg protein. These results demonstrate that estradiol, but not progesterone, inhibits striatal dopamine uptake by decreasing the affinity of the transporter for dopamine. Such a mechanism may serve as one of the bases for the modulatory effects of estradiol upon the nigrostriatal dopaminergic system. © 1998 Elsevier Science B.V.

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1. Introduction

It was first suggested that gonadal steroid hormones affect the nigrostriatal dopaminergic system when cases of chorea were reported during pregnancy and following the administration of oral contraceptives (Gamboa et al., 1971; Barber et al., 1976). Since these reports, animal studies have demonstrated that the gonadal steroid hormones estradiol and progesterone do in fact modulate functioning of the nigrostriatal dopaminergic system (Maus et al., 1990; Ramirez et al., 1985). Estradiol, in particular, has been shown to have effects on the nigrostriatal dopaminergic system independent of the presence of other hormones (Bedard et al., 1981; van Hartesveldt and Joyce, 1986). When female animals are ovariectomized and treated with estradiol, changes are seen in the synthesis, metabolism, and release of dopamine in the striatum, as compared with ovariectomized, non-treated animals. While there is no change in overall dopamine content in the striatum after estradiol treatment (di Paolo et al., 1985; Morissette et al., 1990b; McDermott et al., 1994), there is an increase in dopamine turnover, revealed by increases in tyrosine hydroxylase activity (Pasqualini et al., 1995) and in the dopamine metabolites homovanillic acid and dihydroxyphenylacetic acid (di Paolo et al., 1985). It has also been shown that estradiol, when delivered in a pulsatile manner, increases striatal dopamine release in vitro (Becker, 1990a) and continuous estradiol infusion potentiates amphetamine-stimulated dopamine release from striatal tissue of female rats (Becker, 1990b). In vivo estradiol treatment potentiates both basal and potassium-stimulated dopamine release from female mouse striatum when superfused in vitro (McDermott et al., 1994), and increases amphetamine-stimulated dopamine release and rotational behavior in 6-hydroxydopamine lesioned rats (Becker, 1990b).

The increased extracellular dopamine reported in these studies can be due to increased dopamine release, which may result from enhanced synthesis of dopamine, and/or an inhibition of dopamine reuptake by estradiol. It has been proposed that one important function of estradiol is to act as an uptake blocker in the striatum (Ramirez, 1983). This speculation is supported by reports that estradiol blocks dopamine uptake, presumably through the uptake transporter, as evidenced in cerebral cortex (Michel et al., 1987), thalamus (Wirz-Justice et al., 1974) and hypothalamus (Endersby and Wilson, 1974). This proposed mechanism is not universally supported since there are reports of increased dopamine uptake in hypothalamic tissue

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(Cardinali and Gomez, 1977), and data demonstrating an increase in the number of dopamine uptake transporters in the rat striatum after both acute and chronic estradiol treatment (Morissette et al., 1990a; Morissette and di Paolo, 1993). In the present report, we attempt to more directly address this issue through measurements of the kinetics of striatal dopamine uptake in response to estradiol. Since dopamine reuptake through the dopamine uptake transporter is the primary mechanism for clearing dopamine from dopaminergic synapses (Horn, 1979), thereby terminating the action of dopamine, the potential modulation of this process by estradiol could represent an important action exerted by this gonadal steroid hormone. Moreover, it has been demonstrated that dopamine uptake inhibitors have differential effects as a function of brain area (Jones et al., 1995), and the issue of estrogenic modulation of the kinetics of dopamine uptake in the striatum has not yet been addressed. Therefore, the purpose of this study was to determine whether 17β-estradiol inhibits striatal dopamine uptake. To accomplish this goal, the dose-dependent relationship and specificity of estradiol upon the affinity and activity of dopamine uptake transporters was assessed in striatal synaptosomal preparations from ovariectomized rats.

2. Materials and methods

2.1. Methods for synaptosomal preparation and measurement of [^{3}H]dopamine uptake were as that described previously by Boja et al. (1992)

Briefly, striata were rapidly dissected from ovariectomized (> 14 days) female Sprague–Dawley Rats (Zivic Miller Labs., Zelienople, PA) and homogenized in ice cold 0.32 M sucrose using a glass–teflon homogenizer. The homogenate was centrifuged at 800 × g for 10 min, the supernatant collected, recentrifuged at 20 000 × g for 10 min, and resuspended in 0.32 M sucrose to a concentration of 10 mg/ml. The assays were performed in modified Kreb's Ringer Phosphate buffer (126 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.4 mM $MgSO_4$, 16 mM sodium phosphate, 2 mg/ml dextrose, 0.2 mg/ml ascorbic acid, pH = 7.4).

2.2. IC_{50} determinations

Uptake inhibition assays were performed for 17β-estradiol (water-soluble, 49 mg estradiol/g 2-hydroxypropyl-β-cyclodextrin, Sigma, St. Louis, MO) and progesterone (water-soluble, 82 mg progesterone/g 2-hydroxypropyl-β-cyclodextrin, Sigma). Both steroid hormones were complexed to cyclodextrin to increase their solubility in the assay buffer. Identical concentrations of 2-hydroxypropyl-β-cyclodextrin (RBI, Natick, MA) were used in control assays to test for inhibition properties of this solubilizer. Assay tubes contained 1 μM pargyline, 1 nM [^{3}H]dopamine, 0.1 mg striatal synaptosomes, and either estradiol or progesterone in a range of 12 concentrations (100 μM–30 nM) or cyclodextrin alone. Mazindol (1 μM) was used to determine nonspecific uptake. Each concentration was performed in triplicate. Synaptosomes were incubated at 30°C for 10 min in the presence of the drug, before the initiation of the assay. The assay was then initiated with the addition of [^{3}H]dopamine and incubated for 3 min.

2.3. V_{max} and K_m determinations

The assay tubes contained pargyline (1 μM), 0.1 mg synaptosomes, increasing concentrations of [^{3}H]dopamine (10, 20, 40, 50, 100, 200, 400, 500 nM), and either 100, 10, or 0 (control) μM estradiol for a final volume of 1 ml. Mazindol (1 μM) was used to determine nonspecific uptake. The assay was initiated with the addition of the tissue and was incubated for 3 min at 30°C.

Both assays were terminated with the addition of 5 ml ice-cold 0.32 M sucrose, followed by immediate filtration using Whatman GF/B filters soaked in 0.05% polyethylenimine. The filters were washed three times with 5 ml 0.32 M sucrose and the radioactivity was counted using a Beckman LS 6500 scintillation counter. Protein determinations were performed using the methods of Bradford (1976).

2.4. Analyses

IC_{50} values were calculated using Equilibrium Binding Data Analysis (EBDA, Biosoft, Ferguson, MO), while K_m and V_{max} values were calculated with linear regression. Statistical analyses were performed using STATVIEW. An ANOVA was performed to test for differences in V_{max} and K_m among groups, with Fischer's Protected Least Significant Difference test used for all post-hoc comparisons.

3. Results

17β-estradiol inhibited the high affinity uptake of dopamine with an IC_{50} of 7.2 ± 0.6 μM (n = 4). Neither

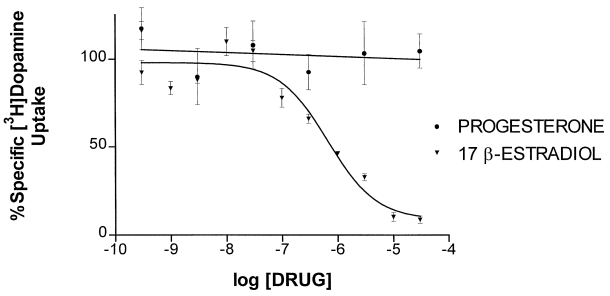

Fig. 1. Inhibition curves of 17β-estradiol (n = 4) and progesterone (n = 3) showing inhibition of [^{3}H]dopamine uptake into striatal synaptosomes from ovariectomized rats. The IC_{50} of 17β-estradiol as derived from these curves was 7.2 ± 0.6 μM. Neither progesterone nor the solubilizing agent 2-hydroxypropyl-β-cyclodextrin (data not shown) inhibited the uptake of [^{3}H]dopamine.

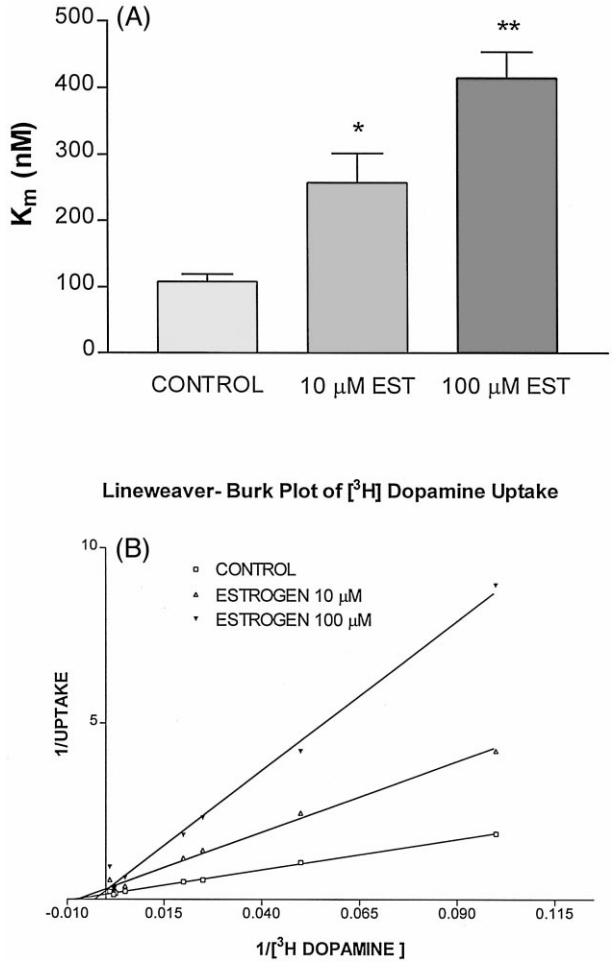

Fig. 2. (A) The K_m values of [^{3}H]dopamine uptake in the absence of estradiol (control, $N = 5$), or in the presence of 10 μM estradiol ($n = 4$) or 100 μM estradiol ($n = 4$). The K_m of each group was significantly different from each other ($P < 0.05$), denoted by $*$. Values are shown as the mean of all trials $\pm$ S.E.M. (B) Lineweaver–Burk plot of [^{3}H]dopamine uptake kinetics in the absence of ($n = 5$) or presence of 10 μM ($n = 4$) or 100 μM ($n = 4$) estradiol. Each point represents the mean of all trials.

progesterone nor the solubilizing agent 2-hydroxypropyl-β-cyclodextrin (data not shown), inhibited the uptake of [^{3}H]dopamine (Fig. 1). The addition of 10 μM estradiol significantly ($P < 0.01$) increased the K_m value for [^{3}H]dopamine from 108.2 $\pm$ 11.4 nM (control, $n = 5$) to 257.8 $\pm$ 43.8 nM ($n = 4$). Likewise, in the presence of 100 μM estradiol the K_m was further increased to 415.0 $\pm$ 39.6 nM ($n = 4$), with levels obtained being significantly greater than both the 10 μM estradiol ($P < 0.01$) and control ($P < 0.0001$) (Fig. 2A). In contrast to the effects of estradiol upon the K_m of dopamine uptake, neither the addition of 10 μM estradiol (8.3 $\pm$ 0.5 pmol/min per mg protein) nor 100 μM estradiol (7.3 $\pm$ 0.8 pmol/min per mg protein) significantly altered the V_{max} of [^{3}H]dopamine uptake from control values (9.2 $\pm$ 0.8 pmol/min per mg protein) (Fig. 2B).

4. Discussion

Our results show that estradiol competitively inhibits striatal DA uptake with an IC_{50} of 7.2 μM. This inhibition results from a dose-dependent change in K_m, but not V_{max}, suggesting a decrease in the affinity, but not the number or function, of dopamine transporters. The effect shows a relative specificity for estradiol, with no inhibition seen in the presence of progesterone, a gonadal steroid hormone known to have effects on striatal function (Ramirez et al., 1985), or with the solubilizing agent cyclodextrin. These results also suggest that estradiol inhibits the transporter through a non-genomic mechanism of action. This latter conclusion follows from the rapidity of the effect obtained, which is often used as a criteria for non-genomic actions (McEwen et al., 1990) and the paucity of estradiol receptors in the striatum (Stumpf and Madhabananda, 1976).

The dose-related increase in K_m but not V_{max} seen in this study is in agreement with data showing that an estrogen homologue, ethinylestradiol, inhibited dopamine uptake by increasing the K_m of the transporter, without changing the V_{max} in rat frontal cortex (Michel et al., 1987). Our results differ somewhat from the observation of Morissette et al. (1990a), who reported an increase in the number of striatal dopamine uptake binding sites within 15–30 min after an acute injection of estradiol, as assessed using [^{3}H]GBR 12935. The difference between this study and our current data may be due to several factors; including but not limited to the dose of estrogen, the experimental conditions (in vitro vs. in vivo estradiol administration), and/or the labeled compound used. Within our experiment, a 10 μM concentration of estradiol was tested. By contrast, the exact concentration of estradiol within the striatum with the in vivo administration protocol of Morissette et al. (1990a) was not determined. The present study employed in vitro techniques exclusively, while those reported by Morissette et al. (1990b) were a combination of in vivo estrogen administration followed by in vitro binding. A number of factors can influence dopamine transporter function and/or [^{3}H]GBR 12935 binding when an agent is administered in vivo. Effects such as alterations of non-dopaminergic neuronal input (Miller, 1983), enzyme induction (Chevillard et al., 1981), induction of non-dopaminergic [^{3}H]GBR 12935 binding sites and alteration of the dopamine transporter by stress (Abercrombie et al., 1989) can all accompany in vivo administration. Some of these factors, such as a potential alteration of non-dopaminergic inputs, may play an important role in the effects of estradiol on the striatum. However, other factors such as the induction of non-dopaminergic [^{3}H]GBR 12935 binding sites would only confound the results obtained using this label. Notably, it has been reported that [^{3}H]GBR

12935 labels not only the dopamine transporter, but the piperazine acceptor site as well (Niznik et al., 1990; Allard et al., 1994), suggesting that results obtained with this label may not be entirely specific for the dopamine transporter.

In the rat striatum, the concentration of estradiol has been reported to vary between 1.147 ± 0.202 and 4.595 ± 2.199 nM as a function of different phases of the estrous cycle (Morissette et al., 1992). The striatal concentration of estradiol is second only to that found within the hypothalamus (Bixo et al., 1986), and is significantly higher than that reported for the rest of the brain, which ranges from 0.144 ± 0.030 to 0.719 ± 0.145 nM (Morissette et al., 1992). These levels are also substantially greater than serum estradiol levels (Morissette et al., 1992). It cannot be determined for certain whether these effects of estrogen observed in the present report represent physiological actions of this gonadal steroid, since the degree of dopamine transporter inhibition necessary to produce the biochemical and behavioral effects is not known. The fact that estrous cycle changes are obtained for a number of nigrostriatal dopaminergic functions (Fernandez-Ruiz et al., 1991; Joyce and van Hartesveldt, 1984) would support the idea that some of these actions involve physiological effects. Additionally, our in vitro technique is most useful for determining direct effects of a compound on the dopamine transporter. Using a synaptosomal membrane preparation may disrupt any receptor/second messenger mediated effects on dopamine uptake. For example, it has been shown that estrogen can rapidly affect the activity of various isozymes of protein kinase C, with most reports demonstrating an increase in activity (Bignon et al., 1990; Morozova et al., 1989; Sidorkina et al., 1988). Protein kinase C has been reported to phosphorylate the dopamine transporter, inhibiting dopamine uptake (Copeland et al., 1996; Huff et al., 1997; Zhang et al., 1997). If estradiol does affect the uptake of dopamine via a second messenger system like protein kinase C, our experimental conditions may not be conducive to demonstrating the full inhibition properties of this hormone.

This proposed capacity of estradiol to decrease the affinity of the transporter for dopamine has a number of wide-ranging implications with regard to functioning of the nigrostriatal dopaminergic system. For example, we have recently reported that striatal dopamine release in response to 1-methyl-4-phenylpyridinium infusion is attenuated when estradiol is included in the superfusion medium (Disshon and Dluzen, 1997). This action afforded by estrogen is may be a result of inhibition of the dopamine uptake transporter, since neurotoxic agents like 1-methyl-4-phenylpyridinium (Heikkila et al., 1985) and 6-hydroxydopamine (Schwarting and Huston, 1996) utilize the dopamine transporter for entrance into the neuron terminal, which subsequently results in neuron death. Such a mechanism may underlie the capacity for estrogen to function as a neuroprotectant as seen in response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment to mice (Dluzen et al., 1996a,b) and 6-hydroxydopamine administration to rats (Dluzen, 1997). This speculation is supported by reports that other well-characterized dopamine transporter inhibitors such as mazindol, benztropine, bupropion, amfonelic acid (Ricaurte et al., 1985) and nomifensine (Clark and Reuben, 1995) which have also been found to be protective against the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. This modulation is may be partly involved with the gender differences seen in conditions like Parkinson's Disease (Diamond et al., 1990; Kurtzke and Goldberg, 1988; Mayeux et al., 1992). Although the etiology of Parkinson's Disease remains unknown, the putative neuroprotective capabilities of estradiol may be in part responsible for the gender differences seen in this disease. Estradiol, by decreasing the affinity of the dopamine transporter, may be inhibiting the uptake of an environmental neurotoxin or enhancing dopaminergic transmission. A better understanding of hormonal effects on synthesis, release, metabolism and reuptake of dopamine in dopaminergic systems may shed light on not only the gender differences seen in dopaminergic diseases, but on the disease processes themselves.

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