Dopamine and $GABA_A$ Receptor Imbalance after Ovariectomy in Rats: Model of Menopause

Roger Bossé, Thérèse Di Paolo

School of Pharmacy, Laval University, Quebec City, Quebec, Canada; Department of Molecular Endocrinology, CHUL Research Center, Laval University Medical Center, Ste-Foy, Quebec, Canada

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A peak of first episodes of schizophrenia can occur in postmenopausal women. Furthermore, tardive dyskinesia is more common in postmenopausal women than in men of comparable age. This study investigated the effect of ovariectomy (2 weeks or 3 months) in rats as a model of decreased gonadal function associated with menopause. After ovariectomy, frontal cortex D_1 receptors progressively decreased in density with no change of affinity over time. Striatal D_1 and D_2 receptors also had decreased density after ovariectomy with no change of affinity. In the substantia nigra pars reticulata, a progressive increase in [^{3}H]flunitrazepam-specific binding associated with $GABA_A$ receptors was observed as a function of time following ovariectomy. It is hypothesized that low prefrontal cortex dopamine activity has implications in negative symptoms of schizophrenia and, furthermore, that GABAergic overactivity in the internal globus pallidus-substantia nigra pars reticulata complex plays a role in tardive dyskinesia. The present results suggest that, by reducing brain dopamine receptors and increasing $GABA_A$ receptors, gonadal hormone withdrawal may predispose to schizophrenia and dyskinesia.

Key Words: dopamine receptors, $GABA_A$ receptors, striatum, frontal cortex, substantia nigra pars reticulata, ovariectomy

INTRODUCTION

Gender differences constitute a possible means of studying the factors that mediate the expression and progression of schizophrenia. Gender differences have been repeatedly observed in clinical and epidemiological studies (Angermeyer et al 1989; Angermeyer and Kühn 1988; Bardenstein and McClashan 1990; Deister and Marneros 1993; Flor-Henry 1985; Goldstein and Tsuang 1990; Gureje 1991; Häfner et al 1989, 1991; Iacono and Beiser 1992; Loranger 1984; McCabe 1975; Nicole et al 1992; Seeman 1982, 1985), and these differences remain when the current criteria for schizophrenia are applied (Angermeyer 1982; Goldstein and Tsuang 1990). Age at onset is 4 to 7 years earlier in men than in women, with a second peak larger and later in women after age 40 to 45 years (Hambrecht et al 1992). Regardless of differences in age of onset, the lifetime prevalence of schizophrenia is the same for both sexes. However, in long-term follow-up, women tend to deteriorate more often than men, specifically in the perimenopausal period (Childers and Harding 1990; Opjordsmoen 1991). After menopause, women seem to require larger doses of neuroleptics and to be more at risk of developing tardive dyskinesia; generally,

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Address reprint requests to: Dr Thérèse Di Paolo, Department of Molecular Endocrinology, CHUL Research Center, 2705 Laurier Boulevard, Ste-Foy, Quebec, Canada G1V 4G2.

women develop more forms of dyskinesia and have dyskinesia of greater severity than men (Seeman 1985; Yassa and Jeste 1992).

Numerous hypotheses have been formulated to account for the gender differences in schizophrenia (Dworkin 1990; Goldstein et al 1990; Lewine 1985; Pogue-Giele and Zubin 1988; Ring et al 1991). This paper focuses on the clinical changes occurring at menopause with respect to schizophrenia and tardive dyskinesia. The aim of this study is to model in animals the gonadal hormone withdrawal occurring at menopause, and also to investigate its effect on brain neurotransmitters. Dopamine (DA) and γ-amino-n-butyric acid (GABA) receptor systems were chosen because of their implications in schizophrenia. Ovariectomy in the rat, as a model of menopause in humans, led to an imbalance of DA and GABA$_A$ receptors. DA receptors decreased in the frontal cortex and striatum, whereas GABA$_A$ receptors increased in the substantia nigra pars reticulata (SNr).

MATERIALS AND METHODS

Animals and surgery

We purchased 100 adult female Sprague-Dawley rats (weight, 200 g to 250 g) from Charles River Canada Inc (St Constant, Quebec, Canada). The rats were housed 2 per cage and maintained at 22°C to 23°C for 3 months on a 14:10 light/dark cycle (lights on from 05:00 h to 19:00 h). They had ad libitum access to rat chow and water. All rats were housed for 3 months and divided into 3 groups. In one group, the rats were ovariectomized at the beginning of the experiment (ovariectomized for 3 months); in the second group, the rats were ovariectomized 2 weeks before they were killed (ovariectomized for 2 weeks); and in the third group, the rats remained intact and were at random stages of the estrous cycle (controls). The rats were ovariectomized under anesthesia (1.5% halothane-air mixture) and killed by decapitation. Their brains were rapidly removed, flash-frozen in isopentane over dry ice, individually wrapped in aluminum foil, and kept at -80°C until dissection and assay.

Binding assays

The striata and frontal cortexes from 2 rats of each group were dissected, homogenized with a glass-Teflon homogenizer in 100 vol (wt/vol) 15 mM Tris-HCl, pH 7.4, and centrifuged at 50,000 × g for 15 min at 4°C. Supernatants were discarded and the pellets were resuspended and centrifuged under the same conditions. Supernatants were discarded and the final pellets were resuspended in 100 vol of incubation buffer (15 mM Tris-HCl pH 7.4, 120 mM NaCl, 20 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1 mM EDTA and 0.01% ascorbic acid). To estimate D_1 and D_2 receptor densities (B_{max}) and affinities (Kd), [^{3}H]SCH23390 (8 concentrations 0.05 nM to 0.75 nM, 79 Ci/mmol, Amersham) and [^{3}H]spiperone (8 concentrations, 0.025 nM to 0.05 nM, 100 Ci/mmol, Amersham) saturation binding isotherms were performed, respectively, on appropriate homogenates as previously described (Di Paolo et al 1982; Lévesque et al 1989). In these assays, 200 µl of membranes (100 µg to 125 µg protein) was incubated in a final volume of 2 ml for 60 min at room temperature. Incubation was stopped by rapid filtration (Cell Harvester M-48R, Brandel Co., Gaithersburg MD) with 3 rapid 3 ml washes of cold buffer through Whatman GF/C fiberglass filters. The filters were placed into scintillation counting vials with 10 ml of scintillation cocktail (FORMULA-989, NEN-DUPONT). Nonspecific binding was estimated using 1 µM of SKF38393 for the D_1 or 1 µM of (+) butaclamol for the D_2 assay, respectively. Ketanserin (50 nM) was also added in the D_2 assay to block 5-HT_2 binding sites. Radioligand binding was quantified in an LKB beta-counter with 60% to 65% efficiency. Protein determination was performed by the method of Lowry et al (1951).

Substantia nigra GABA$_A$ benzodiazepine binding site autoradiography

Brains from 3 rats of each group were immersed in Tissue-Tek (oct compound, Miles Inc Elkhart, IN) at -18°C, mounted on cryostat chucks, and cut into 10-µm-thick coronal-slices. Four consecutive slices were thaw-mounted on chromalun/gelatin coated microscope slides. Slides were vacuum-dessicated at 4°C for 12 h and stored at -80°C. Autoradiography of GABA$_A$ benzodiazepine binding sites with [^{3}H]flunitrazepam (75 Ci/mmol, Amersham) was performed as described by Canonaco et al (1989) with minor modifications. Slide-mounted brain sections were preincubated for 20 min in incubation buffer (50 mM Tris-HCl pH 7.4). The slides were then incubated with 10 nM [^{3}H]flunitrazepam for 45 min at room temperature. To determine nonspecific binding, 10 µM of clonazepam was included in the incubation buffer. After incubation, the slides were placed in racks and washed twice for 2 min in buffer at 4°C. Slides were then dipped in distilled water at 4°C for 10 sec and allowed to air-dry for 12 h. Sections were apposed to Amersham Hyperfilm-^{3}H with calibrated standards (Microscale, Amersham) and exposed for 14 days. The films were revealed in Kodak D-19 developer, fixed in Kodak rapid fixer, and analyzed by computer-assisted video densitometry (RAS 1000, Amersham). Binding data were determined from film optical density.

Statistics

Data were analyzed by analysis of variance (ANOVA) using Staview 4.0 for the MacIntosh computer.

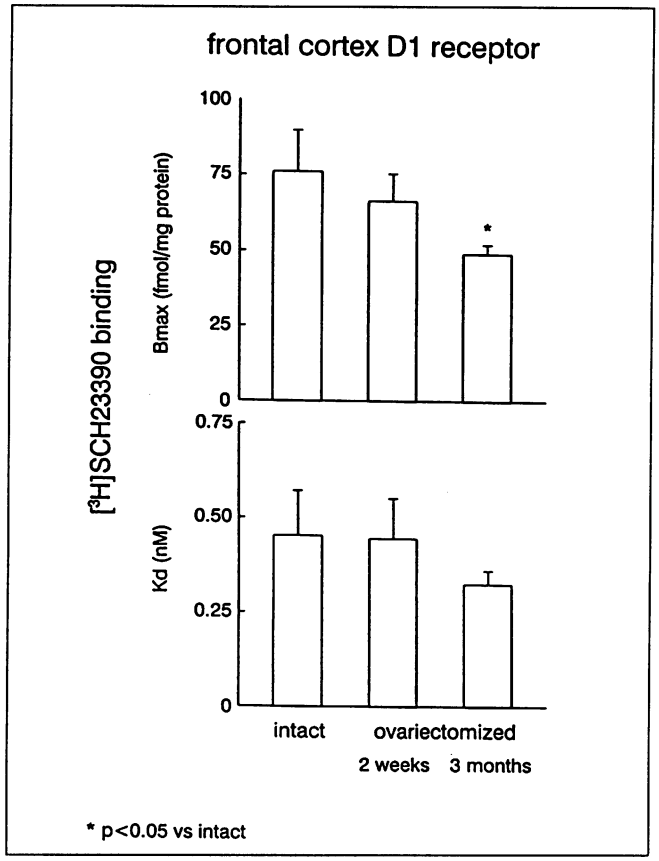

Figure 1. [^{3}H]SCH23390 binding to D_1 receptors in the frontal cortex of intact female rats as well as ovariectomized rats for 2 weeks or 3 months. Results shown are the mean ± SEM of 14 values from 28 rats.

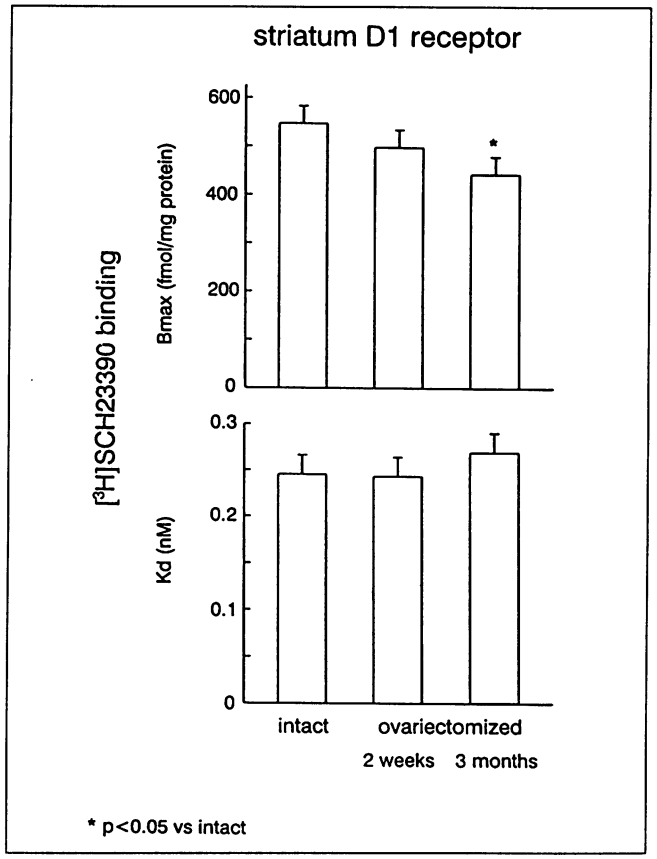

Figure 2. [^{3}H]SCH23390 binding to D_1 receptors in the striatum of intact as well as ovariectomized rats for 2 weeks or 3 months. Results shown are the mean ± SEM of 16 values from 28 rats.

RESULTS

Scatchard plots constructed from saturation experiments using [^{3}H]SCH23390 and [^{3}H]spiperone binding to striatal and/or cortical homogenates were linear, indicating interaction with a single receptor population (not shown). The effect of ovariectomy after 2 weeks and 3 months was a decrease of 14% and 36% ($p < 0.05$), respectively, of frontal cortex D_1 receptor density (see Figure 1, upper panel) and a decrease in striatal D_1 receptor density by 10% and 22% ($p < 0.05$) (see Figure 2, upper panel), respectively, compared with intact female rats. Striatal D_2 receptor density decreased 2 weeks (21%, $p < 0.05$) or 3 months (28%, $p < 0.01$) after ovariectomy compared with intact rats (see Figure 3, upper panel). Ovariectomy did not significantly change striatal or frontal cortex binding affinity of [^{3}H]SCH23390 for D_1 receptors or [^{3}H]spiperone to D_2 receptors (see Figures 1 to 3, lower panels). Striatal D_1/D_2 receptor density ratio was enhanced 2 weeks after ovariectomy (16%, $p < 0.05$) (see Figure 4). In contrast to DA receptors, autoradiography of $GABA_A$ benzodiazepine binding sites showed that ovariectomy progressively increased [^{3}H]flunitrazepam binding in the SNr by 18% (2 weeks after ovariectomy) and 40% (3 months after ovariectomy) ($p < 0.05$), respectively (see Figure 5).

DISCUSSION

The data showed progressive changes in the DA and $GABA_A$ brain receptors of rats over time after ovariectomy. Whereas D_1 and D_2 receptors in the brain progressively decreased, the reverse was observed for $GABA_A$ receptors. To our knowledge, this is the first report of an effect of ovariectomy on frontal cortex D_1 receptors. The decrease in D_1 receptors in the frontal cortex upon gonadal hormone withdrawal is similar to that observed for this receptor in the striatum. Furthermore, these findings are in agreement with our previous observations of striatal D_1 receptors after 2 weeks or 1 month of ovariectomy in rats (Di Paolo 1994; Lévesque and Di Paolo 1990; Lévesque et al 1989). In addition, our results for striatal D_1 receptors are in agreement with the observation of decreased dopamine-stimulated adenylate cyclase in the striatum and nucleus accumbens of

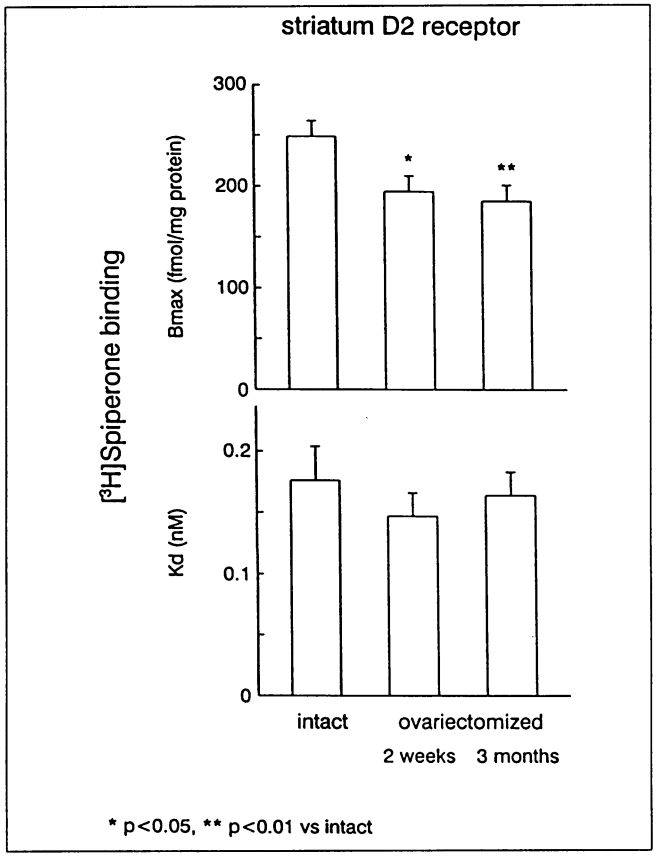

Figure 3. [^{3}H]SCH23390 binding to D_2 receptors in the striatum of intact as well as ovariectomized rats for 2 weeks or 3 months. Results shown are the mean ± SEM of 16 values from 28 rats.

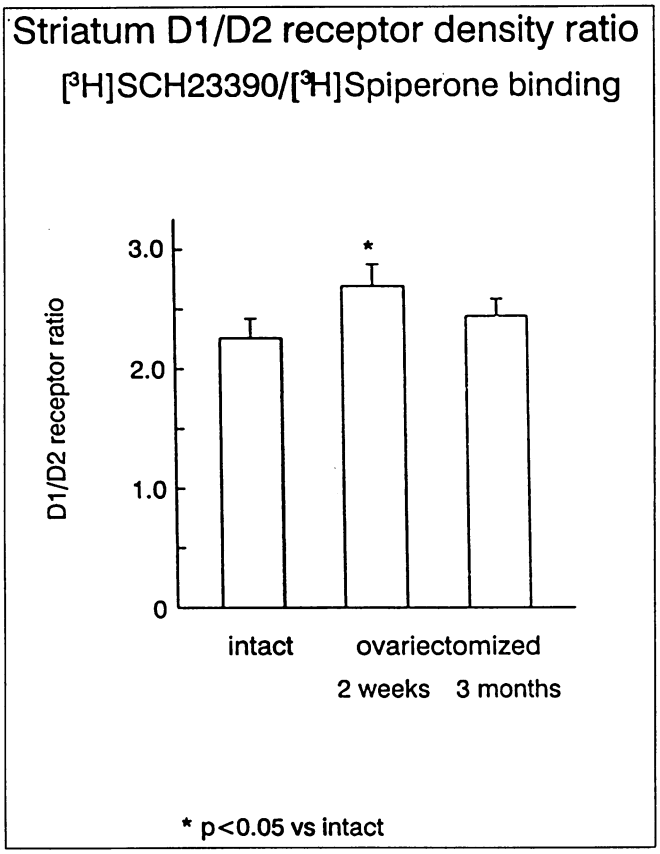

Figure 4. Effect of ovariectomy on the ratio of striatal D_1/D_2 receptor density. Ratios were computed from data of Figures 2 and 3. Results shown are the mean ± SEM of 16 values.

long-term ovariectomized rats (Kumakura et al 1979). Similarly, we also observed that, after ovariectomy, striatal D_2 receptor density decreased with no change in affinity. This finding was somewhat surprising because, in rats showing behavioral supersensitivity to dopamine agonists, the opposite has been reported when they have been ovariectomized for at least 3 months (Fields et al 1991; Gordon and Fields 1989). Long-term ovariectomized rats were shown to have more apomorphine-induced stereotypic sniffing and apomorphine-induced locomotor activity than intact controls (Fields et al 1991; Gordon and Fields 1989). Under our assay conditions, the striatum from 1 animal is required for 1 binding saturation experiment for 1 ligand. Here the striata from 2 rats were pooled to assay both D_1 and D_2 receptors in the same homogenate. Hence, the DA receptors were assayed in the same homogenate to measure the receptor ratio in the same animals. Indeed, ovariectomy increased the striatal D_1/D_2 receptor density ratio.

The earlier hypothesis to explain the development of tardive dyskinesia was based on the concept of supersensitivity at the D_2 receptor level (Gerlach 1988). This supersensitivity is thought to develop as a compensatory response to the chronic blockade of these receptors by neuroleptics that are D_2 receptor blockers. This theory has been supported by various clinical observations. For example, decreasing or discontinuing the neuroleptic drug aggravates dyskinesia (Crane and Naranjo 1971), whereas readministration of neuroleptics ameliorates dyskinesia (Gerlach 1988). However, this theory proved too simplistic and is incongruous with a number of observations of patients with tardive dyskinesia (Fibiger and Lloyd 1984; Gerlach 1988). For example, the number of D_2 receptors in the postmortem brains of tardive dyskinesia patients was not increased compared with those of nontardive dyskinesia patients. By altering D_1/D_2 receptor homeostasis using selective receptor antagonists, several groups have been able to induce dyskinetic syndromes in animals. Rosengarten et al (1983) and Diana and Collu (1990) have shown that stimulation of D_1 receptors induces vacuous chewing in rats and dyskinesias in monkeys. Hence, although D_2 receptor

function is shut down by neuroleptics, D_1 receptors are stimulated by endogenous DA. An imbalance in D_1/D_2 receptor function in the nigrostriatal system could therefore be responsible for the induction of tardive dyskinesia. Indeed, when both SCH23390 (a D_1 antagonist) and raclopride (a D_2 antagonist) are coadministered for 21 days in rats, no apomorphine-induced stereotypy was observed, which suggests no behavioral supersensitivity (Marin et al 1993). In patients with schizophrenia, PET scan studies showed about 65% to 89% of D_2 receptor and no D_1 receptor occupancy with classic neuroleptics, whereas the atypical neuroleptic, clozapine, binds to both D_1 and D_2 receptors with high affinity (Farde et al 1989). Furthermore, this same group also observed that patients suffering from schizophrenia with extrapyramidal side effects have significantly higher D_2 receptor occupancy than those without (Nordström et al 1993). From the human and animal studies summarized above, dyskinesia seems more likely to occur when D_1 and D_2 receptors are not equally blocked, further supporting the importance of a D_1/D_2 imblance in tardive dyskinesia.

Experimental observations gave rise to the concept of 2 distinct pathways from the striatum to the main output station, the globus pallidus-SNr complex, both using GABA as a neurotransmitter (Albin et al 1989; Penney and Young 1986). The DA receptors are located principally on the GABAergic striatal medium spiny output neurons, which constitute more than 95% of all striatal neurons (Gerfen 1992). Interestingly, DA receptors appear to a certain degree to be segregated, in that D_1 receptors are localized mostly in the direct pathway while D_2 receptors are more abundant in the indirect pathway (Gerfen et al 1990; Harrison et al 1990). This DA receptor segregation in the basal ganglia was recently challenged (Surmeier et al 1993) by evidence that D_1 and D_2 family receptors are not strictly segregated in the somatodendritic membrane but are indeed segregated in terminal regions. Based on the available evidence, one can hypothesize that both the direct and indirect output systems of the striatum normally operate in balance, and that after chronic neuroleptic treatment (most with predominantly D_2 antagonistic activity) the equilibrium is lost. Hence, in tardive dyskinesia, it appears that the D_1 response is increased and D_2 activity is decreased. Therefore, the striatal D_1/D_2 receptor imbalance caused by ovariectomy may favor the direct output pathway from the striatum to the SNr. This could influence GABAergic activity in the SNr. Indeed, we have shown that ovariectomy increases [^{3}H]flunitrazepam binding in the SNr.

Hence, hormone withdrawal could affect SNr $GABA_A$ receptors directly or indirectly through changes in the striatum. A direct hormonal effect on the $GABA_A$ receptor complex is also possible considering that the progesterone metabolite 3-hydroxy-5α-dihydroprogesterone can affect in vitro [^{3}H]flunitrazepam binding in the SNr (Canonaco et al 1989, 1993).

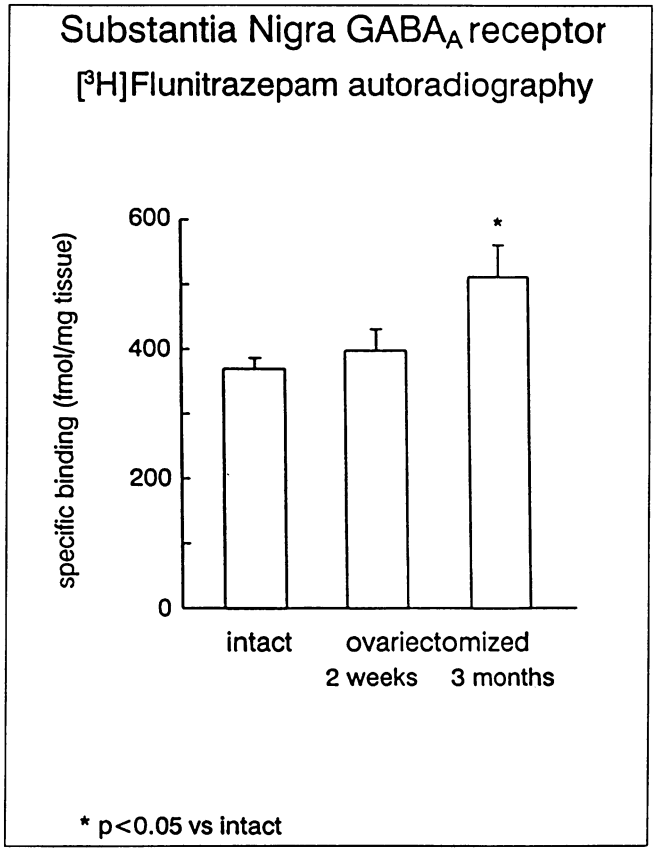

Figure 5. [^{3}H]flunitrazepam (10 nM) binding to the benzodiazepine site associated with $GABA_A$ receptors in the substantia nigra of intact female and ovariectomized rats for 2 weeks or 3 months. Results shown are the mean ± SEM from 3 rats.

The increase in SNr $GABA_A$ receptors after ovariectomy has not been reported previously. However, in the SNr of ovariectomized rats, estradiol treatment decreases [^{3}H]muscimol binding to $GABA_A$ receptors (O'Connor et al 1988). This finding is in accordance with our results supporting a tonic inhibitory role of gonadal steroids in the SNr on $GABA_A$ receptors.

In ovariectomized MPTP monkeys, we recently found (Calon et al 1994) [^{3}H]flunitrazepam binding to be increased in the GPi in animals that developed dyskinesia following long-term pulsatile administration of L-DOPA or U-91356A (a D_2 agonist). In ovariectomized MPTP monkeys and ovariectomized monkeys bearing a midbrain electrolytic lesion, estradiol can inhibit L-DOPA-induced dyskinesia (Gomez-Mancilla et al 1993) or prevent haloperidol-induced dyskinesias (Bédard and Boucher 1986).

Evidence from human and animal studies suggests that all forms of choreic dyskinesia imply a (transient) lowered

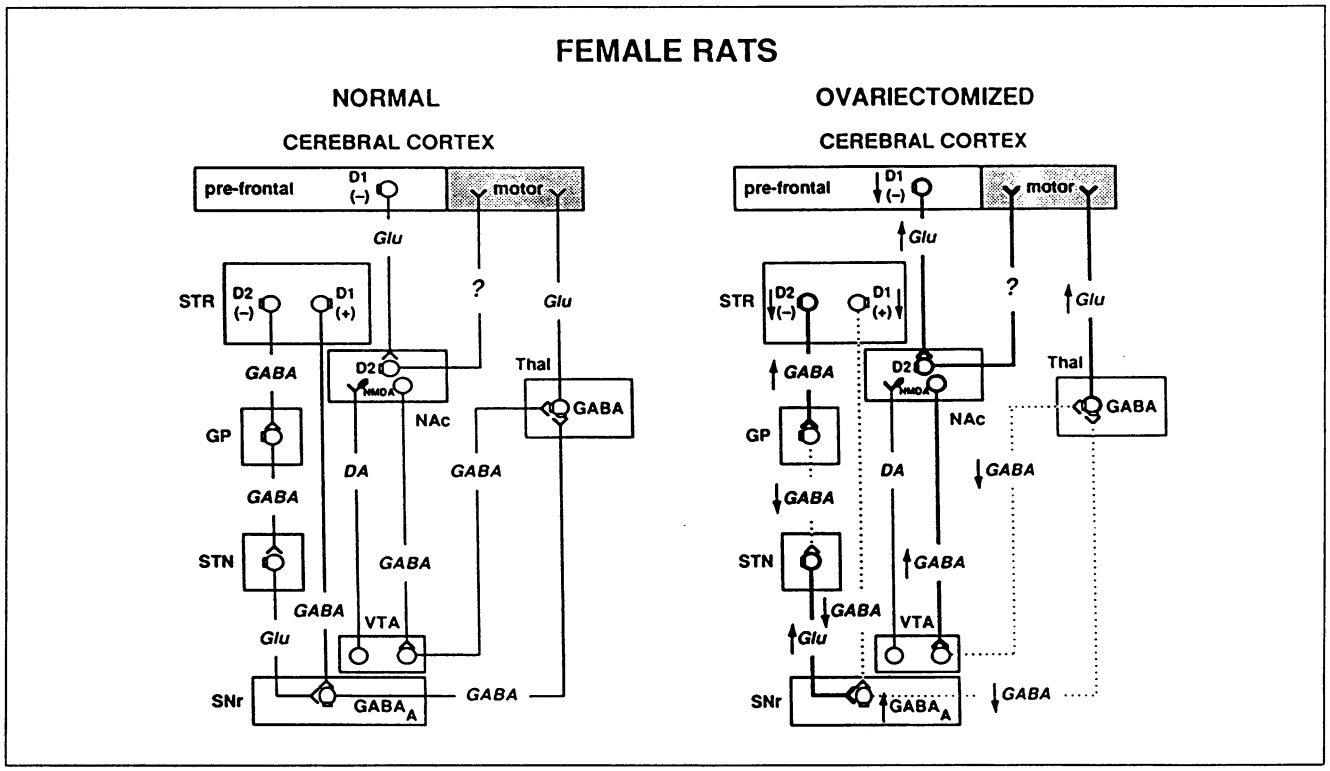

Figure 6. Schematic representation of basal ganglia neurotransmitters in intact and ovariectomized rats with an emphasis on the imbalance caused by gonadal hormone withdrawal. Abbreviations are: GABA: γ-amino-n-butyric acid; Glu: glutamate; GP: globus pallidus; NAc: nucleus accumbens; NMDA: N-methyl-D-aspartic acid; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus; STR: striatum; Thal: thalamus; VTA: ventral tegmental area; ..... decreased activity; _____ normal activity; ▬▬ increased activity.

GABAergic output from the GPi to the thalamus (Albin et al 1989; Crossman 1990; DeLong 1990). Because it is less inhibited, the thalamus innervates the motor cortical regions with increased (glutamatergic) tonus, thus inducing a state of hyperkinesia. We propose that, in ovariectomized rats (as a model of menopause), the D_1/D_2 receptor imbalance in the striatum and/or the increase $GABA_A$ receptors in the SNr led to a decreased GABAergic output to the thalamus, which was then less inhibited and thus overactive, sending excessive glutamatergic signals and rendering the animals susceptible to vacuous chewing movements (or dyskinesia in humans) (see Figure 6).

In support of this hypothesis, rats with vacuous chewing movements induced with haloperidol as a model of dyskinesia have increased [^{3}H]flunitrazepam binding in the SNr (Shirakawa et al 1993), as we observed after long-term ovariectomy.

Low prefrontal cortex dopamine activity in schizophrenia is suggested to cause deficit symptoms (Davis et al 1991). We observed a decrease in D_1 receptors in the frontal cortex of ovariectomized rats. By analogy to menopause, this decrease of D_1 receptors could contribute to a predisposition to the second peak of incidence of schizophrenia in menopausal women (Hambrecht et al 1992).

In summary, ovariectomy, as a model of menopause, decreased D_1 and D_2 receptors in the brain and increased $GABA_A$ receptors, producing an imbalance in neurotransmitter systems upon gonadal hormone withdrawal, which may predispose susceptible individuals to schizophrenia and dyskinesia. A better understanding of steroid-dopamine and steroid-GABA interactions may help to improve dopaminergic drug treatments by taking into account the person's gender and endocrine status. In addition, further characterization of neurotransmitter transmission in the ovariectomized rat may be useful in identifying other changes in the brain at menopause related to mental disorders such as depression, anxiety, and Alzheimer's disease. For example, because the benzodiazepine site is shown here to increase in the SNr, a region involved in the control of movement, it will be interesting to investigate the specificity of this effect in other brain regions involved in mood and cognition. Furthermore, it will be interesting to determine the changes in acetylcholine and

excitatory amino acid receptors and the effects of steroid hormone replacement in relation to Alzheimer's disease.

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