Sex Differences in the Striatal Dopamine D_2 Receptor Binding Characteristics in Vivo

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Objective: *The authors investigated whether striatal dopamine D_2 receptor binding characteristics in vivo are similar in men and women and whether there are sex-related differences in the decline in D_2 receptor density due to aging.* *Method:* *Striatal D_2 receptor density (B_{max}), affinity (K_d), and binding potential (B_{max}/K_d) were measured with positron emission tomography and [^{11}C]raclopride in 54 healthy subjects (33 men and 21 women).* *Results:* *Women had generally lower D_2 receptor affinity than men, and this difference was statistically significant in the left striatum. B_{max} and B_{max}/K_d tended to decline with age twice as fast in men as in women, but the difference did not reach statistical significance.* *Conclusions:* *These results confirm the age-related reduction of D_2 receptor density and binding potential in both sexes in vivo. The lower D_2 receptor affinity suggests an increased endogenous striatal dopamine concentration in women. This may have implications for the differential vulnerability of men and women to psychiatric disorders like schizophrenia and alcohol and substance dependence.*
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Neuroanatomy and neuroimaging studies have revealed gender differences in the volume and morphology of certain brain structures (1–5), cerebral blood flow (6), and glucose metabolism (7–9). Sex differences in behavior and in cognitive and motor abilities have been extensively documented in neuropsychological studies. A consistent finding is that men perform better than women in spatial and motor tasks, whereas women have greater verbal fluency and less functional hemispheric asymmetry than men (10).

Several psychiatric disorders, such as schizophrenia, mood disorders, and alcohol abuse, are thought to be linked to monoaminergic transmission and exhibit gender differences (11–13). However, little is known about the basis of gender differences in monoaminergic transmission in humans. Serotonergic mechanisms have been explored previously by positron emission tomography (PET); and higher 5-HT_2 receptor binding capacity was found in men than in women in several brain regions (14). No consistent gender differences have been reported in dopaminergic transmission in humans. In a postmortem study, dopamine and homovanillic acid (HVA) concentrations were not found to differ between men and women in several regions in the brain (15). On the other hand, in other studies, women had lower dopamine and higher 3,4-dihydroxyphenylacetic acid levels and a higher ratio between this acid and dopamine in postmortem putamen (16) and higher plasma HVA levels (17) than men. In addition, higher HVA concentrations in lumbar CSF were found in women who were postmenopausal or had undergone hysterectomies or ovariectomies than were found in men (18).

While the effect of age on D_2 receptor binding characteristics is relatively well established, the data on gender differences in D_2 receptor characteristics in vivo are inconsistent. Faster age-related decline in D_2 receptors in men (19) and in women (20), as well as no change between the sexes (21), has been reported. In addition, in a postmortem study, striatal D_2 receptor density was reported to decline faster in schizophrenic men than in women (22).

The use of PET has made it possible to study the dopaminergic system in the living human brain. The aim of this study was to assess the effect of gender on the D_2 receptor binding characteristics and to clarify the effect of age on the decline in D_2 receptor characteristics in vivo in healthy men and women through use of PET and [^{11}C]raclopride.

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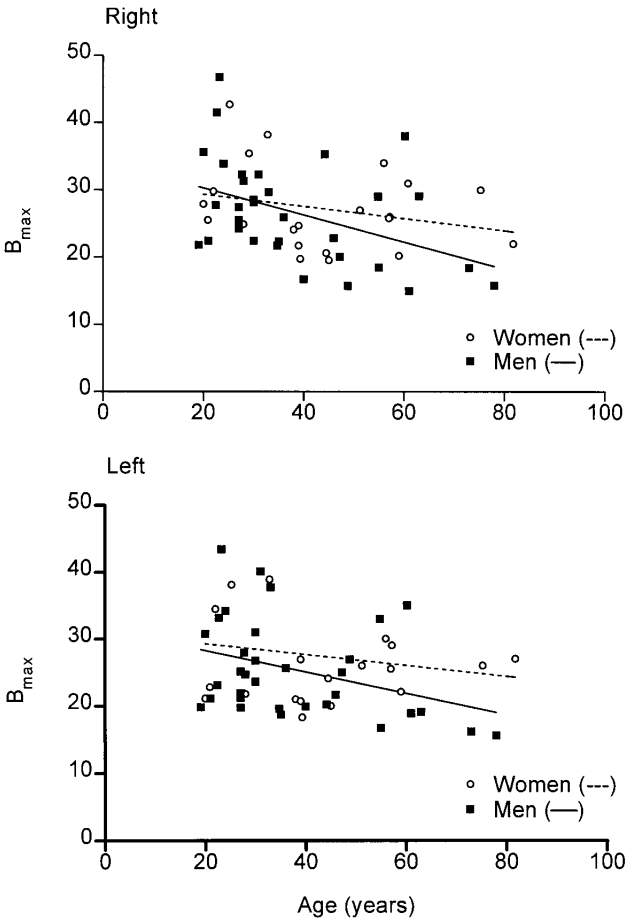
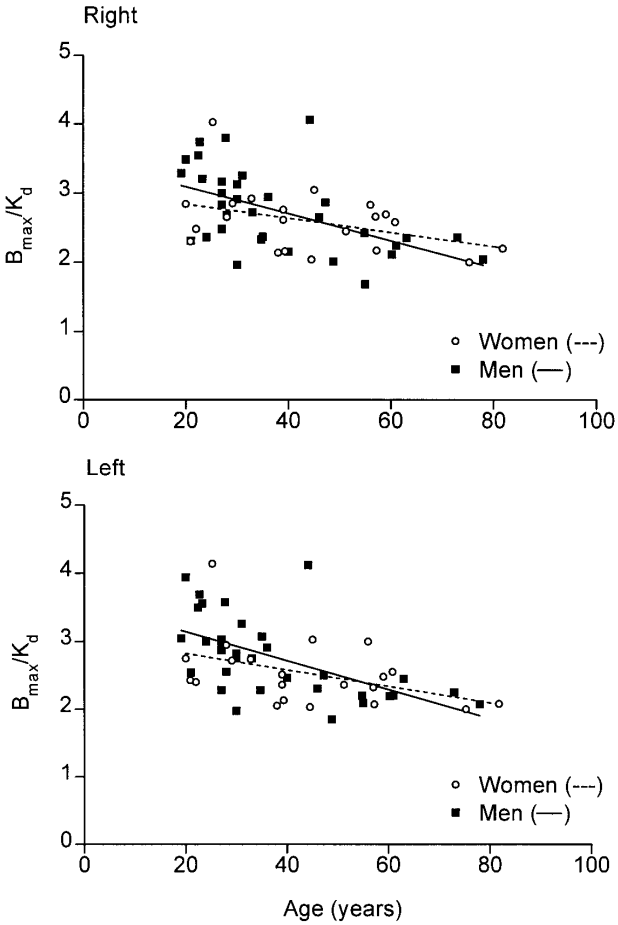
FIGURE 1. Age-Related Decline in the Striatal D_2 Receptor B_{max} in 33 Healthy Men[a] and 21 Healthy Women[b] in the Right and Left Striatum[c]



[a]Right striatum: F=6.91, df=1, 31, p=0.01. Linear regression model was –0.20 × age + 34.4 (r=0.43). Left striatum: F=4.50, df=1, 31, p=0.04. Linear regression model was –0.16 × age + 31.4 (r=0.36).
[b]Right striatum: F=1.29, df=1, 19, p=0.27. Linear regression model was –0.09 × age + 31.2 (r=0.25). Left striatum: F=0.65, df=1, 19, p=0.43. Linear regression model was –0.08 × age + 30.9 (r=0.18).
[c]Sex-by-age interactions were not significant in the right (F=0.98, df=1, 50, p=0.33) or left (F=0.40, df=1, 50, p=0.53) striatum.

FIGURE 2. Age-Related Decline in the Striatal D_2 Receptor B_{max}/K_d in 33 Healthy Men[a] and 21 Healthy Women[b] in the Right and Left Striatum[c]



[a]Right striatum: F=12.43, df=1, 31, p=0.001. Linear regression model was –0.020 × age + 3.49 (r=0.54). Left striatum: F=15.88, df=1, 31, p<0.001. Linear regression model was –0.02 × age + 3.57 (r=0.58).
[b]Right striatum: F=3.58, df=1, 19, p=0.07. Linear regression model was –0.01 × age + 3.04 (r=0.40). Left striatum: F=4.42, df=1, 19, p=0.05. Linear regression model was –0.01 × age + 3.07 (r=0.44).
[c]Sex-by-age interactions were not significant in the right (F=1.37, df=1, 50, p=0.25) or left (F=1.34, df=1, 50, p=0.25) striatum.

METHOD

The protocol was approved by the Ethical Committee of Turku University and University Hospital. A total of 54 healthy Finnish volunteers (33 men and 21 women), ages 19 to 82 years (mean=40.2, SD=16.7), who gave informed consent, were studied. Of the men, 28 were classified as right-handed, three as left-handed, and two as ambidextrous. All women were right-handed. Women were asked about their menopausal status. The subjects were free of major psychiatric and neurologic disorders. None was a regular smoker, and all had normal computerized tomography or 1.5-T magnetic resonance imaging scans of the brain. After a complete description of the study, written informed consent was obtained from all subjects.

The preparation of [^{11}C]raclopride and the quantification of the striatal D_2 receptor B_{max} and K_d, by using the equilibrium approach, were performed as described previously (23, 24). The B_{max}/K_d ratio was calculated as previously described (24).

The statistical analyses were performed with the Systat software package (Systat for Windows, version 5.02, Systat Inc., Evanston, Ill.). Pearson correlation coefficients with probabilities were analyzed for age and receptor binding characteristics. Interactions between age and binding characteristics (homogeneity of regression slopes) for men and women were tested by using analysis of covariance. Homogeneity of group variances was assessed by using Levene's test. Repeated measures analysis of variance (ANOVA) and Student's t test were used in the analysis for differences in B_{max}, B_{max}/K_d, and log-transformed values of K_d between men and women. Bonferroni corrections for multiple comparisons were not applied, since some of the binding characteristics, i.e., B_{max} and B_{max}/K_d, show correlations with each other. The level of statistical significance was defined as $p<0.05$.

RESULTS

B_{max} and B_{max}/K_d, but not K_d, showed a significant decline with age, and the decline was similar in the left and right striatum. The decreases in B_{max} values in the

TABLE 1. Age and Striatal Dopamine D_2 Receptor Binding Characteristics in the Striatum of Healthy Men and Women

	Men (N=33)		Women (N=21)		
Variable	Mean	SD	Mean	SD	p[a]
Age (years)	37.8	16.0	43.9	17.5	0.20
B_{max} (pmol/ml)					
Right	26.7	7.6	27.2	6.3	0.80
Left	25.4	7.2	27.3	7.9	0.36
K_d (nM)					
Right	9.9	2.6	10.6	2.0	0.20
Left	9.4	2.7	11.0	2.9	0.04
B_{max}/K_d					
Right	2.74	0.59	2.59	0.45	0.33
Left	2.76	0.59	2.53	0.49	0.14

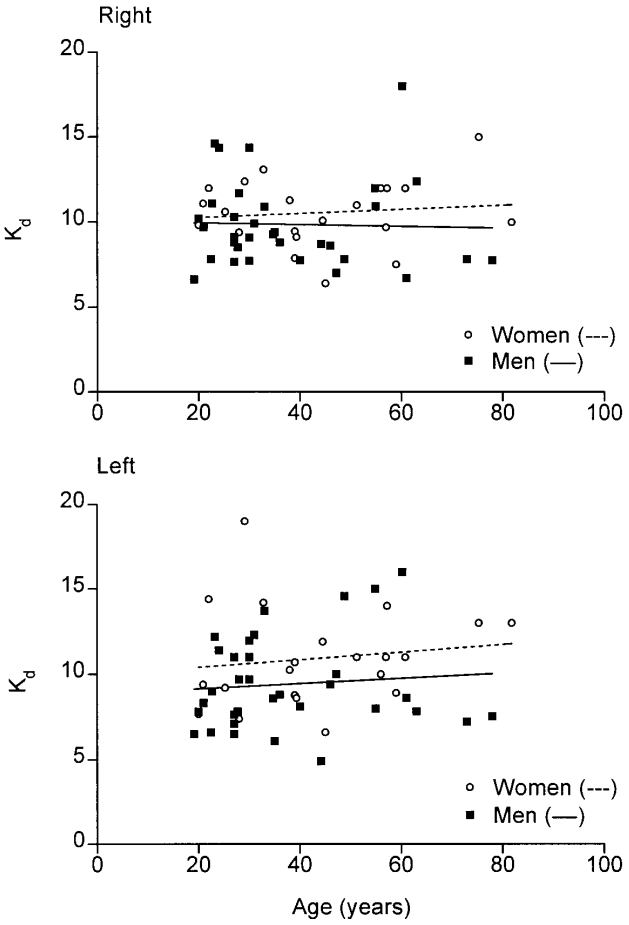
[a]Student's t test.

right and left striatum were 5.0% and 4.0% per decade of life, and the decreases in B_{max}/K_d values were 5.3% and 5.9%, respectively. The Pearson correlation coefficient between B_{max} and age was –0.35 (F=7.2, df=1, 52, p=0.01; estimated regression model=–0.15 × age + 32.80) in the right striatum and –0.25 (F=3.51, df=1, 52, p=0.07; estimated regression model=–0.11 × age + 30.64) in the left striatum. Similarly, the Pearson correlation coefficient between B_{max}/K_d and age was –0.49 (F=16.73, df=1, 52, p<0.001; estimated regression model=–0.016 × age + 3.33) in the right striatum and –0.54 (F=21.54, df=1, 52, p<0.001; estimated regression model=–0.018 × age + 3.40) in the left striatum.

The sex difference in the decline in B_{max} and B_{max}/K_d due to aging was not statistically significant, but there was a trend for these measures to decrease faster in men than in women (figures 1 and 2). While the B_{max} values decreased 6.7% in the right and 5.7% in the left striatum and B_{max}/K_d declined 6.5% in the right and 7.0% in the left striatum per decade in men, the corresponding values for women were 3.1% and 3.0%, respectively, for B_{max} and 3.5% and 4.2% for B_{max}/K_d.

Data on the 33 men and 21 women are presented in table 1. The B_{max} and B_{max}/K_d values did not significantly differ between sexes. However, the D_2 receptor affinity (K_d) was lower in women than in men (figure 3). The gender difference in K_d values was significant in the left striatum (14.5%) (p=0.04) but not in the right striatum (6.7%) (t=–1.29, df=52, p=0.20). Postmenopausal women appeared to have higher K_d values than premenopausal women, but the difference was not statistically significant (table 2). The K_d values in the left striatum were significantly higher in postmenopausal women than in men (18.3%) (t=–2.20, df=39, p=0.03); however, the difference between the two groups in the right striatum was not statistically significant (t=–1.46, df=39, p=0.15). The K_d values of premenopausal women did not differ from those of men. Repeated measures ANOVA did not reveal different left-right asymmetries in men and women. Left-handed men (N=3) tended to have higher left striatal D_2 receptor affinity than right-handed subjects. However, because of the low number of left-handed subjects, no further analysis was attempted.

FIGURE 3. Effect of Gender[a] on Striatal K_d in 33 Healthy Men and 21 Healthy Women



[a]Student's t test was applied to test the significance of difference between men and women in the right (t=–1.29, df=52, p=0.20) and left (t=–2.09, df=52, p=0.04) striatum. Hemisphere-by-sex interaction was not significant (F=1.40, df=1, 52, p=0.24).

Variability of the D_2 receptor binding characteristics was, in general, higher among premenopausal than postmenopausal women (table 2). Levene's test for the homogeneity of the variances in the D_2 receptor binding characteristics between the two groups showed, however, that the variances in the D_2 receptor characteristics were not statistically significant (p values between 0.13 and 0.75) except for the left-side B_{max} values (F=9.72, df=1, 19, p=0.006).

DISCUSSION

Age and D_2 Receptor Binding Characteristics

The results of this study confirm the significant decline in D_2 receptor B_{max} and B_{max}/K_d values as a function of age in human striatum. The effect of aging on the decline in striatal D_2 receptor density, but not affinity, has been firmly documented in humans in postmortem studies of

brains (25–27) and in vivo studies through use of PET (19, 20, 28–31). Similar age-related decreases in the activity of tyrosine hydroxylase (32), levels of dopamine concentration (15, 32, 33), and dopamine uptake (34, 35) have been described, whereas changes in dopa decarboxylase activity have been inconsistent. Some studies have suggested that dopa decarboxylase activity remains unaltered with age (36–38), and others have suggested that it decreases slightly (39).

It has been suggested that the age-related decline in D_2 receptor binding in vivo is different in men and women (19, 20). In a recent in vivo study, covering a relatively narrow age range (20–38 years), neither the D_2 receptor characteristics nor the influence of age was found to be different in men and women (21). In the present study the large age range of subjects, from 19 to 82 years, revealed an age-related decline in D_2 receptor density and binding potential but not in affinity in vivo. B_{max} and B_{max}/K_d tended to decline with age twice as fast in men as in women on average, and a significant age-related decline was found only among men. However, the gender difference in age-related decline in density and binding potential did not reach statistical significance.

Gender and D_2 Receptor Binding Characteristics

Striatal [^{11}C]raclopride binding has been shown to be sensitive to endogenous dopamine fluctuations in several studies in vivo (40–42). This property has been used to assess changes in endogenous dopamine concentration after pharmacological interventions in human brain in vivo (43, 44). In the present study, the lower affinity of [^{11}C]raclopride in women than in men suggests a gender difference in basal endogenous dopamine concentration in the left striatum. This conclusion is based on a reversible ligand-receptor interaction with competition by endogenous dopamine. This results theoretically in elevated K_d and unchanged B_{max} values. It has also been suggested that dopamine noncompetitively inhibits [^{3}H]raclopride binding to D_2 receptors in vitro, thus decreasing B_{max}, while K_d remains unchanged (45). Ross and Jackson (46) observed in their ex vivo study in mice that the reduction of synaptic dopamine concentration with reserpine and γ-butyrolactone reduced K_d values of [^{3}H]raclopride to D_2 receptors because of the competition between dopamine and raclopride. However, the 50% increase in B_{max} values after dopamine depletion by reserpine suggested that a pool of D_2 receptor sites was not available for raclopride to bind when occupied by dopamine. Recent PET studies in monkeys measured with [^{11}C]raclopride and the equilibrium method showed that the reduction of dopamine concentration in brain by reserpine resulted in higher affinity but no change in D_2 receptor B_{max} (47). This corresponds to competitive inhibition between [^{11}C]raclopride and dopamine and supports the interpretation of elevated striatal dopamine concentration in women.

Protein structure may affect the affinity of the ligand for the receptor. Our subjects have been studied for structural mutations in the coding region of the D_2 receptor gene (48). The only subject, a 20-year-old man, possessing protein sequence variation in $Ser^{311}\rightarrow Cys$ showed normal affinity as well as age-corrected B_{max} and B_{max}/K_d characteristics in vivo compared to the mean values of all subjects, indicating that structural variation in the coding region did not cause the gender difference in the present K_d values.

TABLE 2. Age and Striatal Dopamine D_2 Receptor Binding Characteristics in the Striatum of Pre- and Postmenopausal Healthy Women

	Premenopausal Women (N=13)		Postmenopausal Women (N=8)	
Variable	Mean	SD	Mean	SD
Age (years)	32.5	8.9	62.3	10.6
B_{max} (pmol/ml)				
Right	27.3	7.4	27.0	4.6
Left	27.7	10.0	26.7	2.4
K_d (nM)				
Right	10.2	1.8	11.2	2.2
Left	10.6	3.5	11.5	1.7
B_{max}/K_d				
Right	2.68	0.52	2.45	0.29
Left	2.63	0.56	2.36	0.33

The sex-related change in endogenous dopamine concentration may be due to hormonal effects on dopaminergic functioning in the striatum. Gonadal steroid hormones are known to modulate dopaminergic transmission in the rat. Biosynthesis (49), concentration (50, 51), degradation (52), uptake (53, 54), and receptor density (55) of dopamine have been shown to fluctuate during the estrous cycle in the rat. Thus far, such differences in humans have not been confirmed. In a PET study, the binding rate constant (k_3) of [^{11}C]N-methylspiperone to D_2 receptors was reported to fluctuate during the menstrual cycle in women (20). In the current study detailed data on menstrual cycling were not available for all women; however, the effect of menopausal status was analyzed by separately comparing the binding parameters of premenopausal and postmenopausal women to those of all men. The variability in B_{max} and B_{max}/K_d values was, in general, larger among premenopausal than postmenopausal women, probably because of fluctuation in gonadal steroid hormones during the menstrual cycle; however, this remains to be proven.

The role of gender has become an extensively studied variable in schizophrenia research in the last decade. Numerous studies have noted differences in the age at onset, treatment response, course of illness, and outcome between men and women (11, 56, 57). The present results may bear relevance to a gender difference in schizophrenia. The prognosis of schizophrenic women is regarded as better than that of men, and female patients maintain a higher level of social functioning. Similarly, it has been indicated that men are more likely than women to be affected by negative symptoms of schizophrenia. Because positive (psychotic) symptoms of schizophrenia may derive from overactivity of the

dopaminergic system, the current antidopaminergic antipsychotic drug treatment may be better targeted for women and therefore improve the prognosis.

Schizophrenic symptoms appear to correlate with low levels of estrogen across menstrual cycle (58, 59). These observations suggest that estrogen protects against the development of schizophrenia in female subjects (11, 60, 61). Biochemical and behavioral studies in animals have demonstrated that estrogen modulates dopaminergic transmission in striatum; however, both activating and inhibiting effects have been documented. In women, the main effect of estrogen is thought to be antidopaminergic, but the mechanism underlying this interaction is poorly understood. Our data on the lower affinity of [^{11}C]raclopride in women than in men suggest a gender-related difference in synaptic dopamine concentration in the left striatum. The increased dopamine concentration in vivo, especially in postmenopausal women, supports the view that loss of estrogen has a facilitative effect on dopaminergic transmission. According to the dopamine hypothesis of schizophrenia/psychosis, this may have implications for increased vulnerability for psychotic disorders in elderly women, since women are at higher risk than men, e.g., to develop late-onset schizophrenia (62, 63).

The difference in the dopamine D_2 system may also affect vulnerability to alcoholism. Alcoholic men have been reported to have a low striatal D_2 receptor density (24, 64). It can be speculated that higher dopamine tone in women may play a role in lower vulnerability to alcohol dependence in women. Our results are consistent with the fact that the male to female ratio for alcohol-related disorders is about 2 to 1 or even 3 to 1.

Finally, the gender difference in D_2 receptor affinity should be regarded as a preliminary finding, since the difference did not remain significant when a Bonferroni correction for multiple comparisons was applied. Further studies, including also detailed endocrinological data, are required to delineate the basis of variation in endogenous dopamine concentration between men and women. This may shed light on biological liability factors in psychiatric disorders like schizophrenia and alcohol and substance dependence.

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