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Short Communication

Oestradiol Enhances the Vulnerability Threshold for Schizophrenia in Women by an Early Effect on Dopaminergic Neurotransmission

Evidence from an Epidemiological Study and from Animal Experiments

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Summary. In a representative sample of 392 first hospital admissions for schizophrenia from a population of 1.5 million we assessed the "true" age of onset by a semi-standardized interview "IRAOS". We demonstrated that the mean age at onset of the disease is 3–4 years higher in females than in males, with the lifetime risk being exactly equal. In males, the rates of onset show a steep increase – starting from school age and reaching their maximum value in the age group 15–24 years – followed by a steady decrease. Females reach the first peak with a clear delay between 20 and 29 years. After the decrease, a second smaller peak is observed consistently in females within the age group 45–49 years and over. After having excluded competing explanations, we hypothesized that the effect of oestradiol on the dopaminergic system enhances the vulnerability threshold, which is lowered again during the menopause. Alternatively, we assumed that testosterone reduces the vulnerability threshold and thus furthers the earlier onset of the disease in males. We tested the hypotheses in three animal models by examining the effect of gonadal hormones on haloperidol-induced catalepsy and on apomorphine-induced stereotypies in both neonatal and adult rats. No clear influence by testosterone was shown. Oestradiol caused a significant reduction of both dopamine-agonist and dopamine-antagonist induced behaviour. The effects were stronger in neonatal rats. Since oestradiol caused the dopamine (DA) receptor affinity for sulpiride to be reduced by a factor of 2.8, we assumed that the behavioural changes due to oestradiol were accounted for by a down-regulation of DA receptor sensitivity. The higher age at onset and the second peak of onsets after menopause in females may therefore be due to a functional effect and possibly also to an additional structural effect of oestrogens already exerted on the development of the brain.

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Introduction

A substantial body of evidence indicates that a gender-specific factor might modulate the onset and possibly the earlier course of schizophrenia. Data collected by a transnational case register study (Häfner et al. 1989) and data from a representative sample of 392 first-admitted schizophrenics out of a population of 1.5 million (Häfner et al. 1991) indicate that the mean age at first admission is 4–6 years higher, the mean age at true onset is 3–4 years higher in females than in males, independent of the operational definition of the first signs or symptoms of the disease. In spite of this difference in age at onset, the cumulative lifetime prevalence for schizophrenia was equal for both sexes in either study based on the transnational case register data and on the sample of 392 first-admitted patients with a clinical diagnosis of schizophrenia (Fig. 1). The advantage of a delayed onset in women, which seems to be present from early youth, is apparently lost from the beginning of menopause on. Looking at the age distribution of onsets, we found a second peak of first episodes after the age of 45 years in females, also with each definition of true onset used (Fig. 2).

The course of schizophrenia measured by the number of positive or negative symptoms and by functional impairments seems to be more favourable in females only over a few years and to be equal afterwards (Häfner 1987; Seeman and Lang 1990). These observations suggest that oestrogens enhance the vulnerability threshold for schizophrenia, independent of the underlying cause

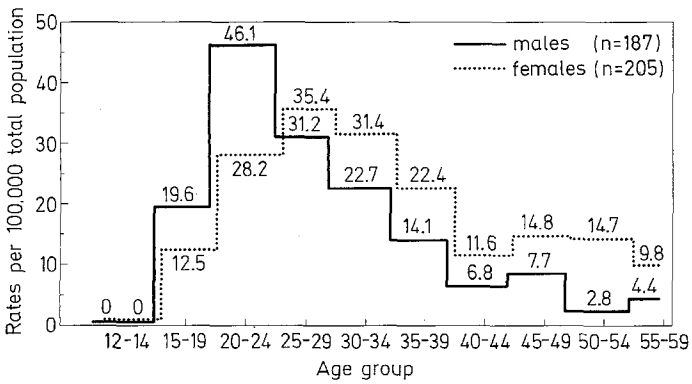

Fig. 1. Sex-specific age distribution at first admission with schizophrenia broad definition (ICD 295, 297, 298.3 and .4). Rates per 100,000 of the population in the corresponding age group. Source of data: Representative 2-year first admission sample (1988–89) Catchment area: Mannheim, Heidelberg, Rhine-Neckar-County, Eastern Palatine

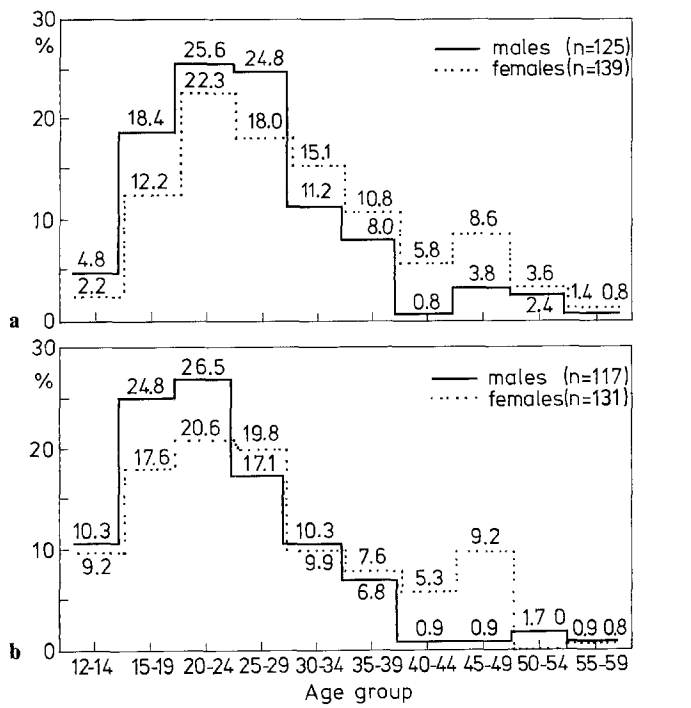

Fig. 2a, b. Sex-specific age distribution according to patient information **a** at time of earliest sign of a mental disturbance (as stated by patient in a free-answer question)

of the disease, probably by the different effects acting on the developing brain and the adult brain.

A Hypothesis

Because of these data, we hypothesized that in women the higher level of oestrogen might have a protective effect on the onset and the occurrence of both positive and negative symptoms in the early course of schizophrenia, by enhancing the vulnerability threshold until the menopause. In principle, part of the gender differences – with exception of the second peak of onsets in females after menopause – could also be due to a lowering of the vulnerability threshold caused by testosterone in males. Indeed, the gonadal hormones testosterone and oestradiol have been found to affect dopaminergic neurotransmission in adult animals. In several studies, mainly of limited methodological rigor, the onset of schizophrenic symptoms has been reported to occur more frequently during periods in which oestrogen levels are low (Seeman and Lang 1990). This observation seems to be valid in the consistently higher proportion of "late-onset schizophrenia" in women compared with men (Bleuler 1943, 1972; Huber et al. 1979; Harris and Jeste 1988; Häfner et al. 1991a).

To test our hypothesis, which is based on the epidemiological findings, we examined the effect of chronic and subchronic application of oestradiol and testosterone on dopamine (DA)-mediated behaviour in some usual animal models of schizophrenia. We investigated the effects of oestradiol in rats during brain development as well as in adult animals.

Testing the Hypothesis by Experiment

In our first experiment 44 newborn Wistar rats were divided into three groups: 14 were ovariectomized and received subcutaneous (s.c.) oestradiol implants (OVX-oestradiol group); 13 were ovariectomized and received s.c. placebo implants (OVX-placebo group); 17 were sham-ovariectomized receiving s.c. placebo implants (sham-OVX group).

Ovariectomy was performed on day 6 postnatal and hormonal treatment was carried out over 2 months when animals reached adult age. Immediately afterwards the behavioural effects of a DA antagonist (haloperidol-induced catalepsy) and of a DA agonist (apomorphine-stimulated stereoptypies, apomorphine-inhibited grooming and sitting behaviour) were compared among the three groups.

Oestradiol antagonized the effects of both haloperidol and apomorphine (Table 1). These effects were more pronounced in OVX-oestradiol rats, which also showed higher oestradiol plasma levels as compared with sham-OVX animals (data not shown).

Table 1. Haloperidol-induced catalepsy (in seconds) and apomorphine-induced behaviour in neonatal treated female rats (means ± SEM)

	OVX + placebo ($n = 13$)	OVX + oestradiol ($n = 14$)	Sham-OVX ($n = 17$)
Catalepsy	237.0 ± 23.0	119.0 ± 12.0***	169.0 ± 18.0*
Oral stereotypies	39.7 ± 1.9	25.1 ± 2.3***	33.0 ± 1.9
Grooming	19.2 ± 1.8	29.2 ± 2.5**	24.7 ± 1.7*
Sitting	24.6 ± 7.2	40.9 ± 6.7	38.4 ± 5.1

OVX, Ovariectomized rats; * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ in comparison to OVX + placebo

Table 2. Haloperidol-induced catalepsy (in seconds) and apomorphine-induced behaviour in adult treated female rats (means ± SEM)

	OVX + placebo ($n = 6$)	OVX + oestradiol 0.25 mg/kg ($n = 8$)	OVX + oestradiol 1.0 mg/kg ($n = 8$)
Catalepsy	230.0 ± 38.0	172.0 ± 49.0	174.0 ± 28.0
Oral stereotypies	38.1 ± 0.8	37.9 ± 0.9	34.6 ± 1.0*
Grooming	29.9 ± 3.0	25.0 ± 3.0	27.4 ± 5.0
Sitting	16.6 ± 3.9	20.0 ± 2.4	33.4 ± 5.6*

OVX, Ovariectomized rats; * $P < 0.05$, in comparison to OVX + placebo

Adult rats were treated subchronically (over 4 days) with s.c. oestradiol in two different daily doses (0.25 and 1.0 mg/kg). The effects of oestradiol on DA-mediated behaviour were similar but less pronounced compared with rats treated neonatally, although the plasma levels of the hormone in the former were 15 times higher than in the latter.

To investigate the effects of testosterone – possibly responsible for lowering the vulnerability threshold in males – we performed the same behavioural experiments in neonatally castrated animals treated subsequently with testosterone or with placebo as compared with a sham-castrated group. No conclusive effect of testosterone was observed.

The Protective Effect of Oestradiol Seems To Be Mediated by a Down-regulation of D_2 Receptors in the Brain

Our experiments demonstrate that oestradiol significantly reduced the behavioural changes caused by a DA agonist as well as the motor effects of a DA antagonist in neonatal rats and with a weaker effect also in adult rats. To clarify the effect of oestrogen on DA neurotransmission, we examined the postmortem striatal [^{3}H] sulpiride binding in the prepared brain tissue. We found no difference in the number of binding sites among the three neonatal groups. However, K_d was 2.8 times higher in the oestrogen-treated compared with the OVX-placebo group, thus suggesting a lower receptor affinity to [^{3}H] sulpiride in the oestrogen group. The enhanced vulnerability threshold due to oestrogen is therefore presumably a result of a down-regulation of dopaminergic receptors by oestradiol. In the adult animals, no clear differences could be found between placebo- and oestrogen-treated groups of ovariectomized animals with regard to B_{max} and K_d.

A potent antidopaminergic activity of short-term oestradiol treatment has been reported in experimental animals (Labrie et al. 1978; Raymond et al. 1978). Acute administration of oestradiol was found to increase plasma prolactin concentrations and DA turnover in the striatum (DiPaolo and Falardeau 1985), to enhance neuroleptic-induced catalepsy (Fields and Gordon 1982), and to increase DA receptor (D_2) density (Hruska 1986). Our present findings suggest that chronic oestradiol administration promotes changes in receptor sensitivity that attenuate both antagonistic and agonistic DA activity, whereas we could find no evidence for changed receptor density.

Two Components of the Oestrogen Effect: an Early Structural and a Later Functional Effect Fading Out After the Menopause?

The considerable difference between the inhibition of DA-mediated behaviour by oestradiol in neonatally ovariectomized and verum-treated rats as compared with animals ovariectomized and treated when adults points to the marked effects of physiological concentrations of the hormone on brain maturation and differentiation of DA neurons during the early development of the CNS.

The antidopaminergic activity of oestradiol has also been shown in humans. Therapeutic efficacy of oestradiol was reported in clinical conditions characterized by an increased DA activity such as levodopa-induced dyskinesias (Bédard et al. 1977) and tardive dyskinesia (Villeneuve et al. 1980). Moreover, oestradiol has been found to precipitate neuroleptic-induced parkinsonism, suggesting an enhancement of dopaminergic blockade in the striatum (Sovner and DiMascio 1978).

Discussion

Epidemiological and clinical evidence suggests an influence of oestrogen levels on the vulnerability threshold for schizophrenia. We have already demonstrated the clearly slower increase in youth and the higher incidence of schizophrenia after the menopause in women, thus adding to the lower cumulative risk for schizophrenia by that age the number required to reach the same lifetime risk as males by the age of 60. Some studies with hospital populations – still needing an epidemiologically sophisticated replication – seem to indicate increased rates of relapse with schizophrenic women within the menstrual cycle when oestrogen levels are low, such as during and before menstruation (Seeman and Lang 1990), or during the postpartum period (Kendell et al. 1987), whereas relapse rates seem to be low during pregnancy, when oestrogen levels are high (Chang and Renshaw 1986). In view of the general trend of these findings, it is tempting to hypothesize that the limited protective action of oestrogens in schizophrenia is mediated by down-regulating the D_2 receptor sensitivity, similar to the effect of antipsychotic drugs blocking DA neurotransmission. Both reduce the probability of the occurrence of schizophrenic symptoms or the triggering of a psychotic episode by precipitating events probably by enhancing the vulnerability threshold. This does not affect the true lifetime risk of the disease. The results of our study provide direct experimental support for this assumption and suggest that other preventive or therapeutic compounds enhancing the vulnerability threshold for schizophrenia

may well be found having less undesirable side-effects than neuroleptics and hormones.

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