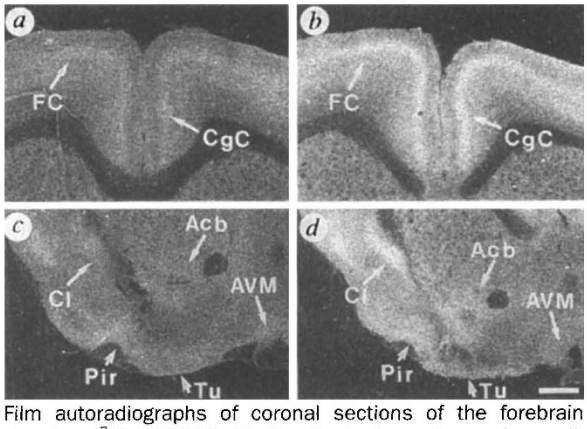
Oestrogen and mental state

SIR — Oestrogen is thought to exert powerful effects on mood, mental state and behaviour in women. Here we show that an acute surge of oestrogen in the female rat induces a significant increase in the density of 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors in higher centres of the forebrain, suggesting that this may be a key mechanism in the psychotropic effect of oestrogen. The role of oestrogen in affective disorders (depression and mania) is suggested by the fact that menopausal and postnatal depression are associated with a massive drop in plasma oestrogen concentrations, and oestrogen has been reported to be effective in the treatment of depression in women[1–5]. Differences in the age of onset and symptoms of schizophrenia in women compared with men has also implicated oestrogen in schizophrenia[6–8].

Affective disorders have long been attributed to defective serotonin transmission. Psychopharmacological data suggest that defective serotonin transmission may also be responsible, at least in part, for schizophrenia in that 'atypical' antipsychotics such as clozapine and risperidone, which are highly effective in the treatment of schizophrenia, bind with much greater affinity to 5-HT$_{2A}$ than to dopamine receptors[9–11]. Oestrogen, in its positive-feedback mode for triggering the ovulatory gonadotrophin surge, stimulates a threefold increase in the amount of 5-HT$_{2A}$-receptor messenger RNA in the dorsal raphe nucleus of the female rat[12]; indeed, a single pulse of oestrogen significantly increases the density of 5-HT$_{2A}$ binding sites in cerebral cortex and the nucleus accumbens[13]. These findings were based on autoradiography using as ligand [^{3}H]ketanserin in the presence of prazosin (to block binding to α_1-adrenoreceptors). Because of their potential importance it was crucial to verify these results with a highly selective 5-HT$_{2A}$ ligand, RP62203 (ref. 14).



Film autoradiographs of coronal sections of the forebrain showing [^{3}H]RP62203 binding in brain regions of an oil-treated (*a*, *c*) compared with an oestradiol benzoate-treated (*b*, *d*) ovariectomized rat. FC, frontal cortex; CgC, cingulate cortex; Cl, claustrum; Acb, nucleus accumbens; Pir, piriform cortex; Tu, olfactory tubercle; AVM, anteroventral periventricular nucleus region and medial preoptic area combined. Dark-field photography; scale bar, 1 mm.

[^{3}H]RP62203 BINDING IN BRAIN REGIONS OF OVARIECTOMIZED RATS TREATED WITH OESTRADIOL BENZOATE (OB) OR VEHICLE (OIL)

Brain region	Oil-treated	OB-treated	Per cent increase caused by OB	Paired *t* test (*P*)	Wilcoxon signed rank test (*P*)
Anterior frontal cortex	159.3 ± 17.4	200.7 ± 17.5	26	0.0010	0.0156
Anterior cingulate cortex	164.8 ± 14.6	194.4 ± 16.3	18	0.0041	0.0156
Piriform cortex	118.5 ± 14.5	148.0 ± 16.8	25	0.0101	0.0156
Olfactory tubercle	93.9 ± 8.9	108.2 ± 12.7	15	0.0340	0.0312
Nucleus accumbens	113.0 ± 10.7	133.5 ± 13.5	18	0.0332	0.0156
Claustrum	160.7 ± 17.0	168.5 ± 19.0	5	0.1452	0.0781
AVPv region	89.1 ± 5.6	95.6 ± 6.5	7	0.1232	0.0781
MPOA adjacent to AVPv	88.7 ± 5.9	92.4 ± 6.6	4	0.2282	0.0547

The above means (±s.e.m.) were calculated from measurements in three sections per brain region per rat, and six rats per treatment group. Measurements in frontal and cingulate cortex were made on laminae IV and Va where there was the greatest density of [^{3}H]RP62203 binding. The experimental method and quantitative and statistical analysis of autoradiograms were as described in ref. 13 and the binding of [^{3}H]RP62203 determined as described in ref. 15. AVPv, anteroventral periventricular nucleus; MPOA, medial preoptic area.

We now report that oestrogen significantly increases the binding of [^{3}H]RP62203 in anterior frontal, anterior cingulate and the primary olfactory cortex and in the nucleus accumbens (see figure and table), essential brain regions for cognition, emotion, mental state and mood, as well as neuroendocrine control[13]. As with [^{3}H]ketanserin and other 5-HT$_{2A}$ ligands[13], in frontal and cingulate cortex the density of [^{3}H]RP62203 binding sites was greatest in laminae IV and Va.

The concordance between the present [^{3}H]RP62203 effects and our previous[13] findings using [^{3}H]ketanserin[13] provides compelling evidence that the acute effects of oestrogen on mood and mental state are mediated at least in part by an increase in density of 5-HT$_{2A}$ receptors. Our experimental model mimics the changes in plasma oestrogen concentrations that occur during the human menstrual cycle, immediately after parturition and at the time of the climacteric (menopause onset). Because oestrogen also affects expression of the gene for the serotonin transporter[14], the target for highly effective antidepressants such as fluoxetine (Prozac), further investigations are required to determine whether the effect of oestrogen on the 5-HT$_{2A}$ receptor is more pertinent to schizophrenia or to affective disorders.

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