Estrogen Control of Central Neurotransmission: Effect on Mood, Mental State, and Memory

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Received April 3, 1995: accepted May 30, 1995

KEY WORDS: estrogen as psychoprotectant; estradiol-17β; testosterone; aromatase; serotonin; 5-hydroxytryptamine; 5-hydroxytryptamine2 receptors; cerebral cortex; nucleus accumbens; arginine vasopressin; bed nucleus of the stria terminalis; social memory; psychosis: depression: premenstrual syndrome; postnatal depression; schizophrenia; mania; Tourette’s syndrome.

SUMMARY

1. Estrogen exerts profound effects on mood, mental state and memory by acting on both “classical” monoamine and neuropeptide transmitter mechanisms in brain. Here we review an example of each type of action.

2. With respect to the effect of estrogen on central monoamine neurotransmission, low levels of estrogen in women are associated with the premenstrual syndrome, postnatal depression and post-menopausal depression. Sex differences in schizophrenia have also been attributed to estrogen. Previous studies have shown that estrogen stimulates a significant increase in dopamine2 (D2) receptors in the striatum. Here we show for the first time that estrogen also stimulates a significant increase in the density of 5-hydroxytryptamine2A (5-HT2A) binding sites in anterior frontal, cingulate and primary olfactory cortex and in the nucleus accumbens, areas of the brain concerned with the control of mood, mental state, cognition, emotion and behavior. These findings explain, for example, the efficacy of estrogen therapy or 5-HT uptake blockers such as fluoxetine in treating the depressive symptoms of the premenstrual syndrome,
and suggest that the sex differences in schizophrenia may also be due to an action of estrogen mediated by way of 5-HT$_{2A}$ receptors.

3. With respect to the effect of estrogen on central neuropeptide transmission, estrogen stimulates the expression of the arginine vasopressin (AVP) gene in the bed nucleus of the stria terminalis (BNST) in rodents. This results in a 100-fold increase in AVP mRNA in the BNST and a massive increase in AVP peptide in the BNST and its projections to the lateral septum and lateral habenula. The BNST-AVP system enhances and/or maintains "social" or "olfactory" memory, and thus provides a powerful model for correlating transcriptional control of neuropeptide gene expression with behavior. Whether similar mechanisms operate in the human remain to be determined.

4. These two examples of the action of estrogen on central neurotransmission are discussed in terms of their immediate clinical importance for the treatment of depressive symptoms, their use as powerful models for investigations on the steroid control of central neurotransmitter mechanisms, and the role of estrogen as "Nature's" psychoprotectant.

**INTRODUCTION**

Estrogen has long been known to exert powerful effects on brain function. Thus, for example, in spontaneously ovulating mammals such as man, monkey, sheep and rat the ovulatory surge of luteinizing hormone (LH) is triggered by a spontaneous surge of estradiol-17β secreted by the ovary. This estradiol surge acts on the brain and the anterior pituitary gland to initiate a positive feedback cascade which involves the release of the decapeptide, LH-releasing hormone (LHRH), and an increase in pituitary responsiveness to LHRH (Everett, 1988; Fink, 1979, 1988, 1994). Pituitary responsiveness to LHRH is further increased by a unique property of LHRH which is to increase pituitary responsiveness to itself, the "self-priming" or "self-sensitizing" effect of LHRH. The latter coordinates the increase release of LHRH into hypophysial portal blood with the increase in pituitary responsiveness so that both reach a peak simultaneously and thereby ensure a massive ovulatory surge of LH (Fink, 1979, 1988, 1995). The preovulatory surge of estrogen also plays a pivotal role in inducing lordosis in the female (Pfaff, 1980). The action of estradiol in triggering the surge of LHRH is mediated by several neurotransmitter systems and receptors, in particular 5-HT$_{2A}$ (Dow, et al. 1994; Sumner and Fink, 1995a, b), α$_{1}$ adrenoreceptors (Rosie et al. 1993; Sarkar and Fink, 1981), and two pharmacologically distinct dopamine receptors one of which inhibits while the other stimulates LHRH release (Sarkar and Fink, 1981).

Clinical observations suggest that in addition to its role in neuroendocrine control, estrogen and its male counterpart, testosterone, exert powerful effects on mood, mental state, behavior and memory. Thus, the early studies of Dalton (1959) showed that of 276 women admitted to psychiatric hospitals, 46% were admitted at or immediately before menstruation. The incidence of suicide was also much greater during the luteal compared with the follicular phase of the