

# Estrogen Makes the Brain a Sex Organ

Stephen M. Stahl, M.D., Ph.D.

**Issue:** *The explanation of neurobiological actions of estrogen and other sex hormones on the brain is strengthening the link between reproductive hormones and behavior. Estrogen receptors in the brain are quite different from neurotransmitter receptors and appear to influence mood, cognition, and synaptogenesis.*

**I**s estrogen a sex hormone or a neurotransmitter? Estrogen has well-documented actions on several neurotransmitter systems, including serotonergic, adrenergic, and cholinergic pathways and receptors.<sup>1</sup> However, recent advances from molecular neuroscience reveal that estrogen does not appear to act like a traditional neurotransmitter.

Recall that chemical neurotransmission occurs in the synapses between cells and at receptors within neuronal membranes.<sup>2</sup> Information is then relayed from the external membrane to cellular headquarters, namely the DNA in the cell nucleus. Neurotransmitters relay their messages via a chemical pony express of many se-

quential intracellular riders. The last rider is a transcription factor that delivers the information directly to genes, basically telling them to turn on or to turn off.

Estrogen bypasses this process and places a direct call to the genome. That is, it floats directly through the neuronal membrane and the nuclear

membrane, and connects to its estrogen receptors right in the cell nucleus, next to the DNA. No need for the pony express here, for estrogen is itself the transcription factor.<sup>3</sup>

When genes are activated, all sorts of events can occur in a cell. The effects of estrogen on gene expression have been most extensively studied

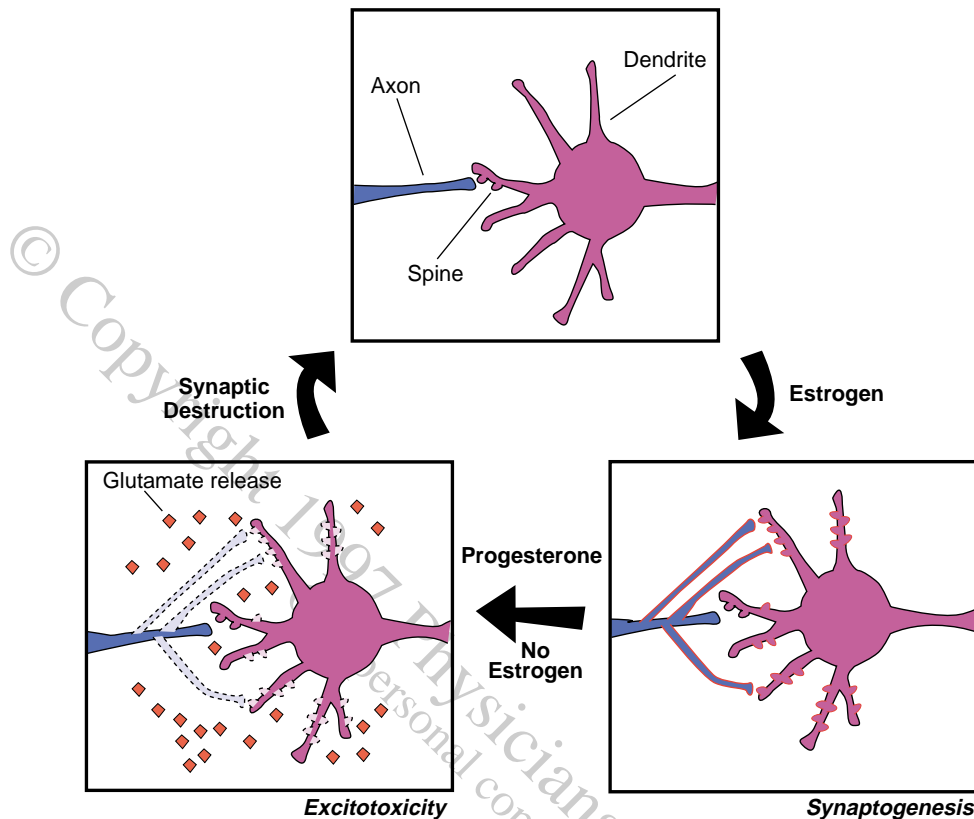
## Take-Home Points

- ◆ Although the effects of estrogen on bone, breast, uterus, and the cardiovascular system are well-known, recent advances are now clarifying our understanding of the influence that sex hormones can have on the brain as well
- ◆ Receptors for estrogen are present in the cell nucleus of certain neurons, where they can directly influence the expression of genes in the central nervous system
- ◆ Estrogen can exert profound cyclical influences upon synapses in certain neurons during the menstrual cycle, with early-cycle estrogen erecting synapses and late-cycle estrogen withdrawal dismantling them

*BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

*From the Clinical Neuroscience Research Center in San Diego and the Department of Psychiatry at the University of California San Diego.*

*Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, 8899 University Center Lane, Suite 130, San Diego, CA 92122.*



in tissues traditionally thought to be the primary targets of this hormone, namely, the reproductive organs, bone, and, indirectly, the cardiovascular system.

Since the consequences of gene expression take a while to develop, the effects of estrogen are long term and not immediate. One of the best examples of delayed gene expression is how estrogen can dramatically alter the cellular machinery for both constructing and dismantling synapses in response to changes in estrogen levels.<sup>4</sup> The building up and tearing down of these synapses take time, but occur within the time course of a single menstrual cycle (see Figure).

The presence of estrogen thus triggers the genetic machinery necessary to build synapses. Perhaps even

more incredibly, the withdrawal of estrogen not only stops further synapse formation, but apparently activates the genetic machinery necessary for tearing apart synapses, perhaps via an excitotoxic mechanism with glutamate.<sup>5</sup>

Exactly how such actions of estrogen alter neurotransmission or behavior is the subject of intense current research activity. Could direct calls to the genome from the transcription factor estrogen interact with the delayed arrival of psychotropic drug-induced pony express transcription factors? Would such interaction alter individual responses to psychopharmacologic treatments? Better understanding of the molecular mechanisms of action of estrogen at its CNS receptors may ultimately impact how

mental health practitioners approach normal behavior and the treatment of psychiatric illness across the life cycle. Certainly, the brain is a very important sex organ. ♦

#### REFERENCES

1. Jensvold MF, Halbreich U, Hamilton JA, eds. *Psychopharmacology and Women: Sex, Gender and Hormones*. Washington, DC: American Psychiatric Press; 1996
2. Stahl SM. *Essential Psychopharmacology*. New York, NY: Cambridge University Press; 1996
3. de Cupis A, Favoni RE. Oestrogen/growth factor cross-talk in breast carcinoma: a specific target for novel antioestrogens. *Trends Pharmacol Sci* 1997;18:245–251
4. Woolley CS, Gould E, Frankfurt M. Naturally occurring fluctuations in dendritic spine density on adult hippocampal pyramidal neurons. *J Neurosci* 1990;10:4035–4039
5. Stahl SM. Excitotoxicity and neuroprotection. *J Clin Psychiatry* 1997;58:247–248