

Effects of Estrogen on the Central Nervous System

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Issue: *Estrogen targets the central nervous system as well as peripheral tissues in women and may be a key regulator of monoaminergic neurotransmission and various behaviors.*

Estrogen's actions in the central nervous system are being clarified. We presented some of these concepts several years ago in a BRAINSTORMS feature¹ and updated our findings of estrogen's actions on its unique nuclear receptors in last month's feature.² Here we illustrate how estrogen interacts with its receptors (Figure 1) and how "cross-talk" between estrogen's actions at its nuclear receptors and its direct and indirect actions at monoaminergic neurons may exert important regulatory effects upon neuronal functioning and behaviors, such as mood and cognition (Figure 2).

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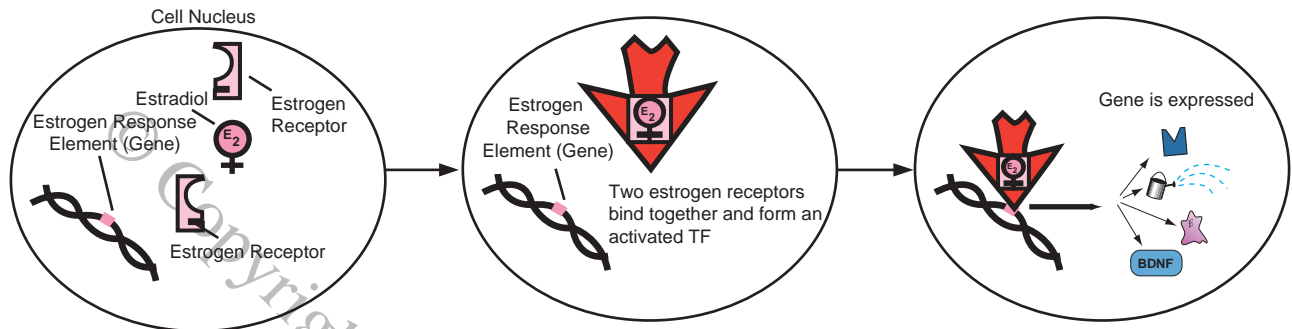
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Take-Home Points

- ◆ Estrogen has important actions in the central nervous system as well as in peripheral tissues such as bone, breast, uterus, and cardiovascular system through its actions on unique nuclear receptors known as nuclear ligand-activated transcription factors.
- ◆ When estrogen acts in the brain, it can lead to the production of neuronal growth factors, as well as enzymes and receptors that facilitate monoaminergic neurotransmission.
- ◆ Actions of estrogen in the central nervous system may impact various behaviors, such as mood and cognition in women.

Figure 1. How Estrogen Interacts With Its Receptors

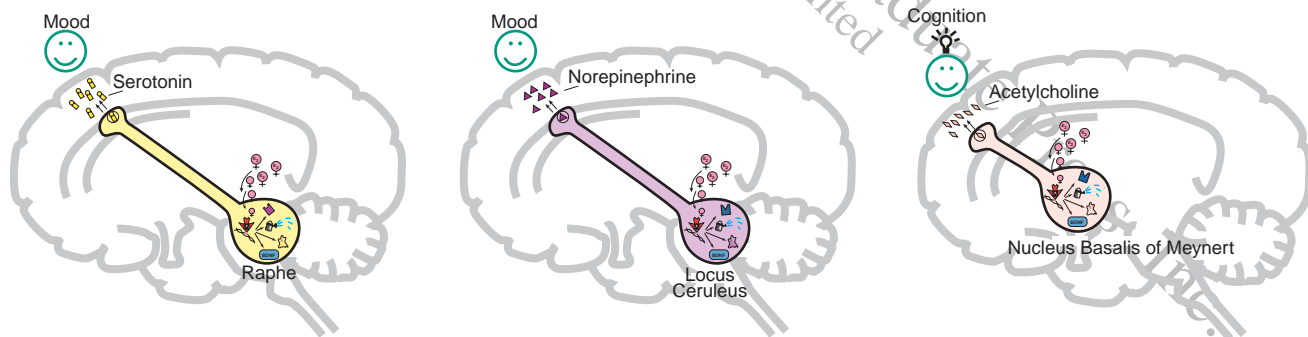


Two copies of estrogen receptors are not currently bound to any estrogen.³ Estrogen receptors are located in the cell nucleus and are members of a large superfamily of receptors known as “nuclear ligand-activated transcription factors.”² Genes, called “estrogen response elements,” can be expressed when activated estrogen receptors bind to them.^{4,5} Estrogen receptors and estrogen response elements exist both in peripheral tissues, such as female genitalia, and in the central nervous system.

Estrogen receptors become activated by binding of estrogen. When 2 copies of estrogen receptors join together,³ the estrogen-receptor combination actually becomes a transcription factor (TF). Transcription factors transcribe genes into RNA, then RNA into proteins. Receptor phosphorylation also regulates the activation of transcription factors.⁶

The interaction of estrogen-receptor transcription factors results in gene expression. Estrogen receptors activated by binding to estrogen become transcription factors that can, in turn, bind directly to the DNA of the estrogen response elements and cause transcription of these genes.³ Numerous genes may be so expressed, resulting in the synthesis of numerous proteins, such as receptors, growth factors, enzymes, brain-derived neurotrophic factors, and many other proteins that regulate cellular functioning.

Figure 2. How Estrogen's Cross-Talk Actions Could Affect Neuronal Functioning and Behavior



Serotonin axons project from mid-brain raphe to frontal cortex.³ In experimental animals, loss of estrogen has been shown to diminish serotonergic functioning and estrogen replacement to potentially boost serotonergic functioning.⁴ This effect of estrogen may be the reason some women respond to serotonergic antidepressants in the presence of estrogen better than in its absence.⁷

Norepinephrine axons project from locus coeruleus to frontal cortex.³ Estrogen may boost noradrenergic functioning and enhance mood in a manner analogous to that shown for serotonin in the previous figure.⁴

Acetylcholine axons project from the nucleus basalis of Meynert to frontal cortex. If estrogen boosts cholinergic function, it may have positive cognitive benefits.⁴