# Molecular Neurobiology for Practicing Psychiatrists, Part 5: How a Leucine Zipper Can Turn On Genes: Immediate-Early Genes Activate Late-Gene Expression in the Brain

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**Issue:** *Neurotransmitters activate genes that activate other genes; that is, neurotransmission can rapidly deploy a strike force of immediate-early genes, like the first troops sent into combat. These early genes then combine to draft an army of genes to mobilize numerous important gene products that alter the function of a neuron targeted by a neurotransmitter.*

This is the fifth and final lesson in our series explaining molecular neurobiology for psychiatrists (see references 1–5). Previous lessons in this series have shown how neurotransmitters can quickly activate genes like c-*fos* and c-*jun* (Figure 1).[3,4] These genes function as rapid responders to the neurotransmitter's input, like the first troops sent into combat once war has been declared. This rapid deployment force of immediate-early genes (IEGs) reacts within 15 minutes of receiving a neurotransmission (Figure 2) by being the first to encode their respective proteins, Fos and Jun. This encoding lasts for only a half hour to an hour, but it is enough time for Fos and Jun, nuclear proteins that live and work in the neuron's cell nucleus, to team up and form a leucine zipper–type of transcription factor. The zipper, in turn, activates many kinds of late-onset genes (Figures 1 and 2). Thus, Fos and Jun serve to wake up the much larger army of inactive genes. Which individual soldier genes are so drafted to active gene duty depends on a number of factors: which neurotransmitter is sending the message, how frequently it is sending the message, and whether it is working in concert with or opposition to other neurotransmitters talking to other parts of the same neuron at the same time.

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## Take-Home Points

- Practicing psychiatrists should become conversant with the vocabulary of molecular neurobiology, because this is now the language describing the biological basis and genetics of mental illnesses.
- The molecular neurobiology of how neuronal genes are activated can also explain the ultimate mechanism of action of numerous psychotropic drugs used in daily practice by psychiatrists.

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Figure 1. How Early Genes Activate Late Genes

At the top, a transcription factor is activating the immediate-early genes (IEGs) c-*fos* and c-*jun*, producing the protein products Fos and Jun, respectively. Once Fos and Jun proteins are synthesized, they can collaborate as partners and produce a Fos-Jun combination protein that acts as a transcription factor for late genes. The Fos-Jun transcription factor is also called a "leucine zipper." The leucine zipper transcription factor formed by the products of the activated early genes c-*fos* and c-*jun* returns to the genome and finds another gene. Since this gene is being activated later than the IEGs, it is called a late gene. The product of the late gene can be any protein the neuron needs, including neurotrophic growth factors, enzymes, and receptors.

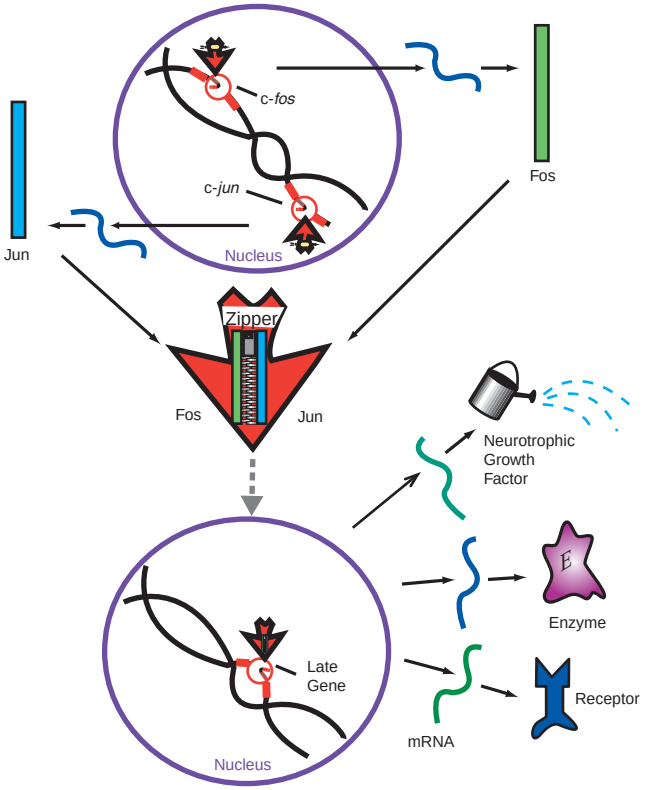


Figure 2. Time Course of Neurotransmitter-Induced Activation of Genes

The earliest events start at the top, and the later events cascade down through the graph. Neurotransmitter binding to receptor is immediate, and many important events occur within the first hour. IEGS are probably activated within 15 minutes and late genes within the first hour. However, it is only many hours to days after activation of the late genes that the profound physiologic actions are seen, such as regulation of enzymes, receptors, and synaptogenesis.