Molecular Neurobiology for Practicing Psychiatrists, Part 4: Transferring the Message of Chemical Neurotransmission From Presynaptic Neurotransmitter to Postsynaptic Gene Expression

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Issue: *Neurotransmitters activate genes in their target neurons by precipitating a molecular cascade, which may be the ultimate consequence of chemical neurotransmission. When this transfer is aberrant, a mental disorder may be manifest. When drugs act upon neurons to change gene expression, this could lead to therapeutic actions, side effects, and the long-term consequences of drug abuse.*

This month's feature is the fourth in our series on molecular neurobiology for practicing clinicians and integrates the first 3 parts[1–3] here as a summary and overview.[4]

Overview

Neurotransmitters precipitate a cascade of molecular events which are carried out by a team of molecular players that interact with one another cooperatively, handing off messages from one molecule to another. This relay accomplishes the transfer of information from the transmitting neuron's neurotransmitter, which is outside the receiving neuron, across the neuronal membrane and into the receiving neuron, resulting in many potential effects upon intracellular processes.

These neurotransmitters, i.e., first messengers, occupy their receptors on the neuronal membrane. Once this extracellular first messenger from the transmitting neuron has handed off to an intracellular second messenger of the receiving neuron, the message penetrates deep inside the recipient cell in a complex molecular cascade reaching enzymes, receptors, ion channels, and, ultimately, DNA to deliver the message of how the neurotransmitter from the transmitting neuron wants to alter cellular function in the receiving neuron. At each point along the way, there is a potential site of action where psychotropic drugs or factors contributing to psychiatric and neurologic diseases can change the orders carried by messengers.

Summary of Processes

The continuing processes of activation, change, and production until the desired end product is achieved begins when neurotransmitters activate genes by producing a second messenger, which seeks inactive protein kinase. When 1 protein kinase is paired with another protein kinase, each with its own regulatory unit (R), they are in their inactive form. When 2 of the second messengers interact with the 2 regulatory units, the units become dissociated and the protein kinases are activated. The enzymes are now ready to phosphorylate other proteins (PO4).

Once activated, protein kinase phosphorylates a transcription fac-

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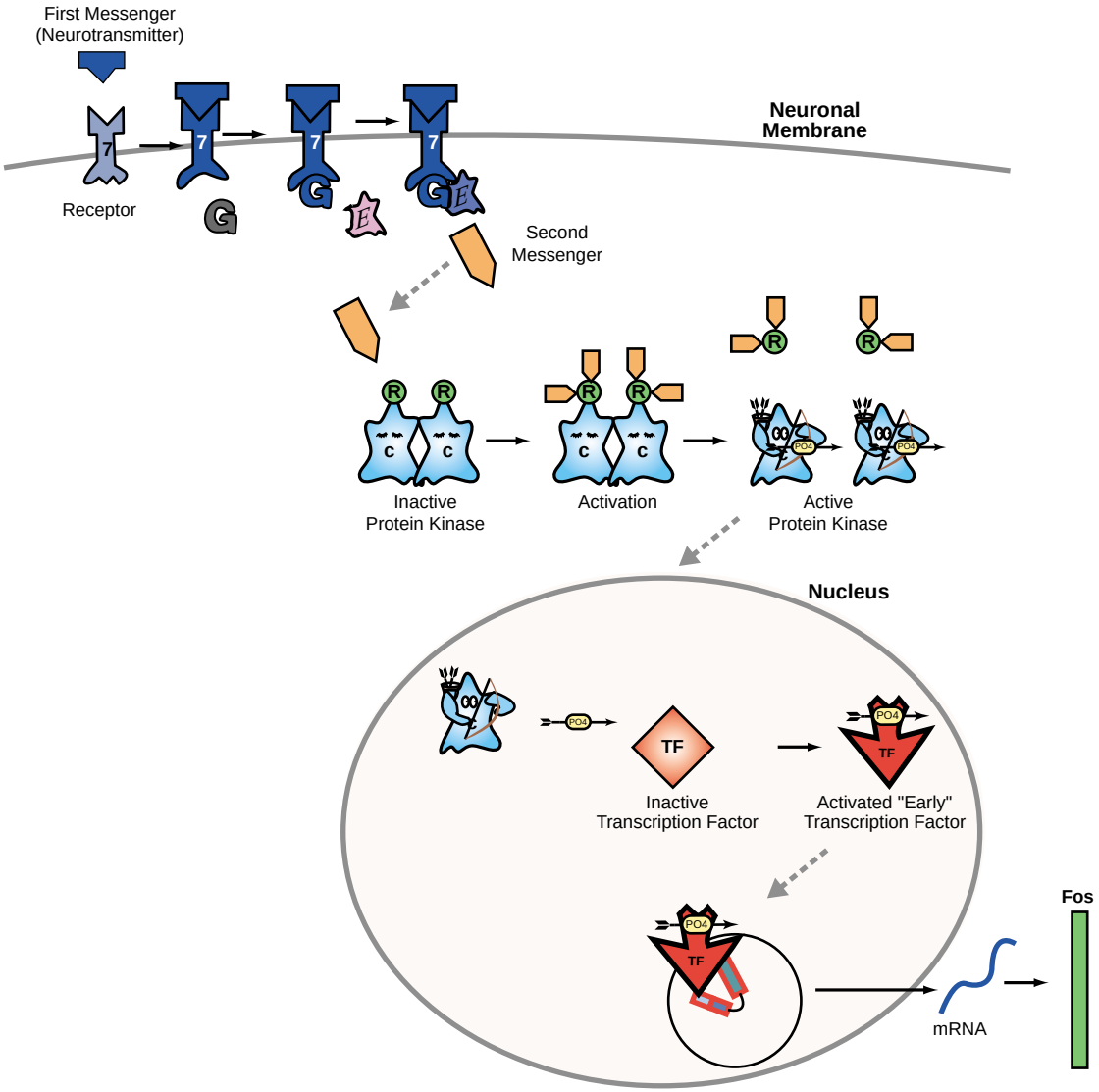
Overview.



tor (TF). Sticking phosphate (PO4) onto the transcription factor activates it so it can bind to the regulatory region of a gene, which in turn activates the gene. The immediate-early gene shown here is called *c*-fos. Activation of a gene means that it is transcribed into RNA; the RNA is then translated into the protein for which it is coded. In this example, the protein is Fos from the gene *c*-fos. Thus, this figure shows a continuous cascade from first messenger neurotransmitter to gene activation and production of the gene product, Fos protein. ◆

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