

Molecular Neurobiology for Practicing Psychiatrists, Part 3: How Second Messengers “Turn On” Genes by Activating Protein Kinases and Transcription Factors

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Issue: *One of the most important advances in molecular neurobiology of relevance to the practicing psychiatrist is how an intracellular second messenger can “turn on” genes by activating first a protein kinase enzyme and then a transcription factor. Failure to turn on the right genes may lead to psychiatric illnesses. Causing the appropriate genes to turn on may be the therapeutic mechanism of action of many current and future psychotropic drugs.*

This is the third in a series on molecular neurobiology for the practicing psychiatrist. Previous lessons provided a visual vocabulary¹ and explained the activation of second messenger systems.² Here we explain the next 3 steps involved in what happens after a second messenger is formed, namely, activation first of an intracellular protein kinase enzyme, then activation of a transcription factor by the protein kinase, and finally, activation of gene expression by the transcription factor.³ The transcription factor is the last element in the cascade of gene activation and can itself cause the gene to “turn on,” i.e., get transcribed into mRNA and then into the important neuronal proteins that regulate neuronal functioning.

Process

Once a second messenger such as cAMP is formed,² it can interact with a family of important regula-

tory enzymes called protein kinases. When cAMP binds to the inactive or sleeping version of a protein kinase enzyme, the enzyme awakens and becomes activated (Figure 1). Protein kinase's job is to activate transcription factors by phosphorylating them (Figure 2). It does this by travelling straight to the cell nucleus and finding a sleeping transcription factor. By sticking a phosphate onto the transcription factor, protein kinase is able to wake up that transcription factor (Figure 2). Once a transcription factor is aroused, it will bind to genes (Figure 3). This in turn wakes up the gene, which is transcribed into mRNA and then into proteins known as gene products (Figure 3).

Summary

Thus, second messengers target the cell to be regulated and alter the synthesis of various molecules inside the cell by activating enzymes, causing them to phosphory-

late proteins and other enzymes. Specifically, to modify the functioning of a neuron, these molecules must alter the genes that control the synthesis of the proteins that implement all of the functions the postsynaptic cell can perform. Eventually the message is passed along via messenger (Figure 1) after messenger (Figure 2) until the information reaches the cell nucleus and the DNA (genes) that are there (Figure 3). Once the message has been received at this site, virtually any biochemical change is possible, since the DNA is the command center of the cell and has all the know-how and power to change any and all biochemical events of which the cell is capable. Therefore, genes do not directly regulate cellular functioning. Rather, they directly regulate the proteins that create cellular functioning. Thus, changes in function have to wait until changes in protein synthesis occur and the events that they cause start to happen. ♦

Figure 1.

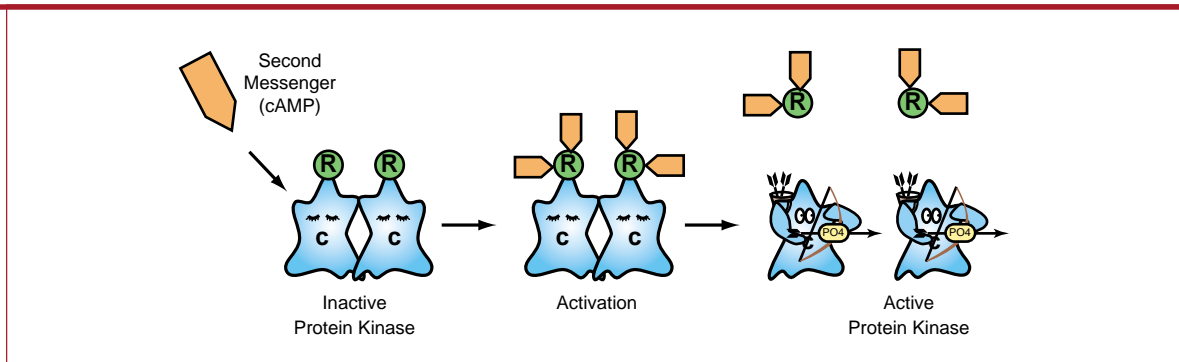


Figure 2.

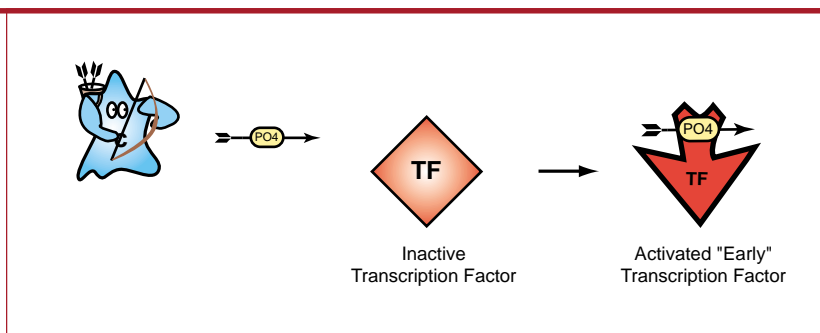
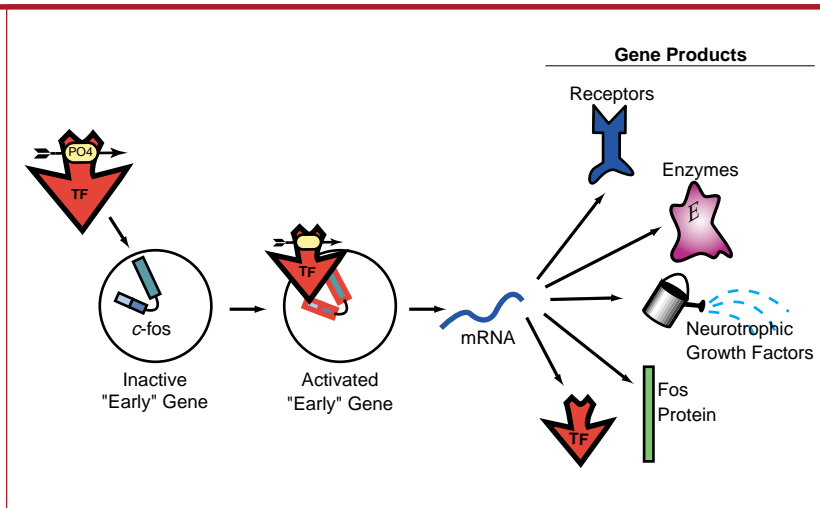


Figure 3.



REFERENCES

1. Stahl SM. Molecular neurobiology for practicing psychiatrists, part 1: overview of gene activation by neurotransmitters [BRAINSTORMS]. J Clin Psychiatry 1999;60:572-573
2. Stahl SM. Molecular neurobiology for practicing psychiatrists, part 2: how neurotransmitters activate second messenger systems [BRAINSTORMS]. J Clin Psychiatry 1999;60:647-648
3. Stahl SM. Essential Psychopharmacology. 2nd ed. New York, NY: Cambridge University Press. In press

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PART 4: TRANSFERRING THE MESSAGE OF CHEMICAL NEUROTRANSMISSION FROM PRESYNAPTIC NEUROTRANSMITTER TO POSTSYNAPTIC GENE EXPRESSION