

## Blue Genes and the Mechanism of Action of Antidepressants

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**Issue:** *Antidepressants may work by triggering a molecular cascade starting with the interaction of monoamines with their receptors and culminating in the up- and down-regulation of critical genes. Neurotransmitter receptor synthesis may be decreased, whereas neurotrophic factors such as brain-derived neurotrophic factor may be increased, leading to an antidepressant response.*

All antidepressants increase neurotransmission for one or more of the monoamines—serotonin, norepinephrine, or dopamine.<sup>1</sup> One problem with the monoamine hypothesis is that the timing of antidepressant effects on neurotransmitters is generally faster (within minutes) than the timing of the antidepressant effects on mood (reaching maximal effect in days to weeks).<sup>1</sup> One theory to explain the ultimate mechanism of delayed therapeutic action of antidepressants is the “neurotransmitter receptor hypothesis of antidepressant action,” which proposes that antidepressants, no matter what their initial actions on receptors and enzymes, eventually cause a desensitization or “down-regulation” of key neurotransmitter receptors in a time course consistent with the delayed onset of antidepressant action of these drugs (Figure 1).<sup>1</sup> This time course coin-

cides with other events, including how long it takes for a patient to become tolerant to the side effects of antidepressants. Thus, desensitization of some neurotransmitter receptors may lead to the delayed therapeutic actions of antidepressants, whereas desensitization of other neurotransmitter receptors may lead to the decrease of side effects over time.

The monoamine hypothesis of antidepressant action on gene expression proposes that antidepressants, no matter what their initial actions on receptors and enzymes, eventually cause critical genes (i.e., “blue genes”) to be activated or inactivated. As already mentioned, some of these are clearly the genes that code for neurotransmitter receptors. Others may be related to neurotrophic factors, such as brain-derived neurotrophic factor (BDNF),<sup>2</sup> as discussed in last month’s BRAINSTORMS.<sup>3</sup> The genetic expression of such neurotrophic

factors may be regulated in part by monoaminergic neurotransmission and stress.

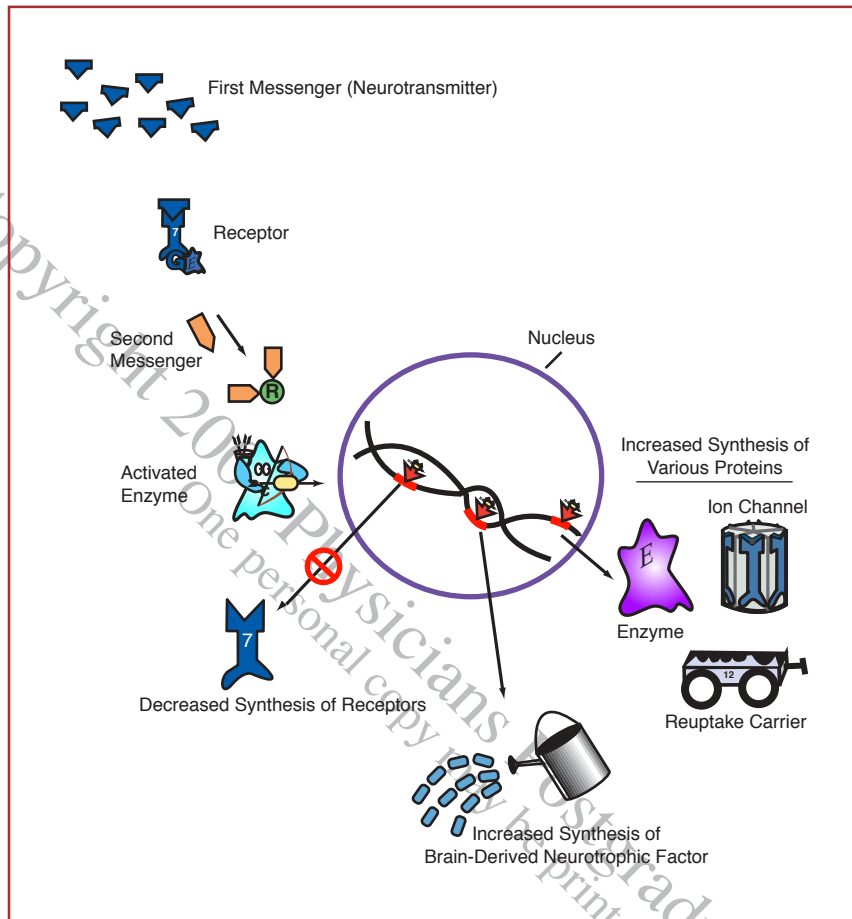
Delayed actions of antidepressants may not only explain the long-lasting therapeutic action of antidepressants, but they may also explain why some patients fail to respond to antidepressants, since it is possible that in such patients the initial pharmacologic actions are not

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Figure 1. Monoamine Hypothesis of Antidepressant Action on Gene Expression



translated into the required delayed pharmacologic and genetic actions. Knowing the biological basis for treatment nonresponse may lead to the development of a greatly needed advance in the pharmacotherapy of depression, namely, an effective treatment for refractory or nonresponding depressed patients. The absence of neurotrophic factors in depression may also explain why, over time and with multiple recurrent episodes, the brain appears to be more likely to relapse into another bout of depression and become more resistant to antidepressant treatments. Also, if one understands the key pharmacologic events that are linked

to the therapeutic actions of the drugs, it may be possible to accelerate these events with drugs in the future. If so, it could lead to another highly desired advance in the pharmacotherapy of depression, namely, a rapid-onset antidepressant.

In summary, all antidepressants have a common action on monoamine neurotransmitters: they boost monoamine neurotransmission, leading to changes in gene expression in the neurons targeted by the monoamines. This change includes desensitization of neurotransmitter receptors, leading to both therapeutic actions and tolerance to side effects. Although antidepressants are classified

on the basis of those actions on neurotransmitter receptors and enzymes that are immediate, attention is increasingly being paid to how these initial and immediate actions translate into delayed actions. ♦

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