Blue Genes and the Monoamine Hypothesis of Depression

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Issue: *Depression may be caused by a stress-induced deficiency in monoaminergic activation of genes that code for neurotrophic factors.*

Although the monoamine hypothesis of depression proposes that depression is due to a deficiency in monoaminergic neurotransmission, no deficiencies in the levels or receptors for serotonin, dopamine, and/or norepinephrine have been consistently reported.[1] Currently, the evolving monoamine hypothesis considers the possibility that depression may be linked to a deficiency in signal transduction from the monoamine neurotransmitter to its postsynaptic neuron in the presence of *normal* amounts of neurotransmitter and receptor. Such a deficiency in the molecular events that cascade from receptor occupancy by neurotransmitter to transcription of genes could lead to a deficient response of target neurons to neurotransmission and thus, depression.

No *single* gene abnormality in depression (i.e., no gene for the blues) to account for flaws in signal transduction has been identified, nor is such a discovery deemed likely.[1,2] Rather, the current thinking is that *multiple* sites in DNA within the genome must interact to cause most depression. Such multiple genes may act independently or additively, or even synergistically; both positive and negative modifier genes, if present, may also influence the likelihood that depression will occur. Thus, unlike Mendelian disorders such as Huntington's disease, in which single genes contribute large effects, depression appears to be caused instead by a complex mixture of multiple genetic vulnerabilities, which may become manifest only if they are combined with specific environmental inputs and perhaps in a critical sequence.[1,2] Thus, probably a whole set of "blue genes" render one vulnerable to depression, not merely a single gene. Depression does not occur unless there is a conspiracy of several genetic and environmental risks. So far, detecting a single conspirator without rounding up all the coconspirators does not have the power to tell how depression occurs on a genetic basis.

New theories that integrate both genetic and environmental risk factors for depression propose that stress, possibly acting through monoaminergic neurotransmission, can cause depression by down-regulating critical genes, so that their key gene products are not produced. One candidate mechanism that has been proposed as a specific site of one of the hypothetical flaws in signal transduction from monoamine receptors is the target gene for brain-derived neurotrophic factor (BDNF) (Figure 1).[3–5] Normally, BDNF sustains the viability of brain neurons (Figure 2).[1,5] Under stress, however, the gene for BDNF is repressed, leading to atrophy and possible apoptosis of vulnerable neurons in the hippocampus when their neurotrophic factor BDNF is cut off (see Figure 2).[1,5] These events in turn lead to depression and to the consequences of repeated depressive episodes, namely, more and more episodes and less and less responsiveness to treatment. The possibility that hippocampal neurons are decreased in size and impaired in function during depression is supported by recent clinical imaging studies showing decreased brain volume of related structures.[5–9]

This hypothesis provides a molecular and cellular explanation of the etiology of depression consistent with a mechanism distal to the neurotransmitter receptor and involving an abnormality in gene expression. Thus, stress-induced vulnerability decreases the expression of genes that make neurotrophic factors, such as BDNF, that are critical to the survival and function of key neurons. A corollary to this hypothesis will be discussed in next month's BRAINSTORMS, namely, that antidepressants may reverse depression owing to their ability to activate the genes for neurotrophic factors.

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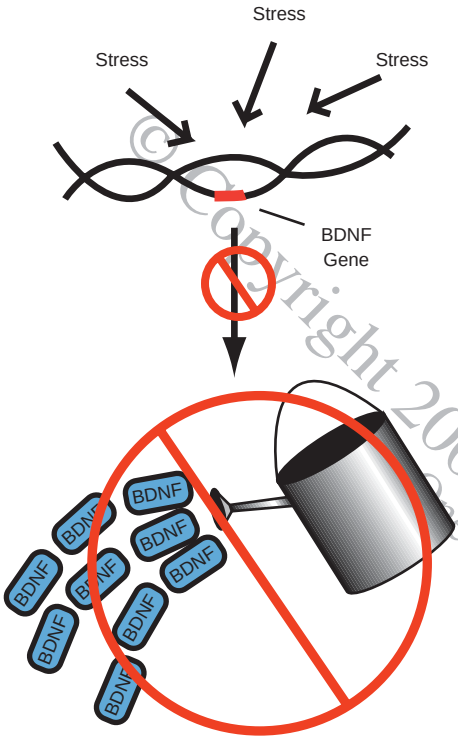
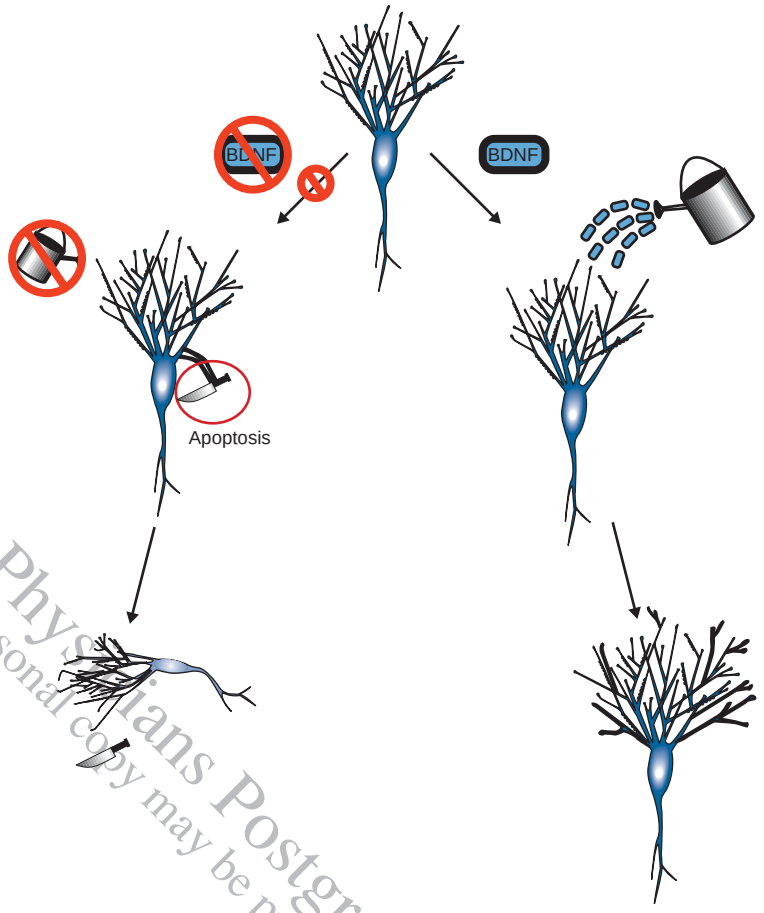
Figure 1. Down-Regulation of Brain-Derived Neurotrophic Growth Factors



One candidate mechanism proposed as the site of a possible flaw in signal transduction from monoamine receptors to genome is the target gene for brain-derived neurotrophic factor (BDNF). Normally, BDNF sustains the viability of brain neurons. Shown here, however, is the gene for BDNF under situations of stress. In this case, BDNF is repressed.

Figure 2. Depression Through Apoptosis



The neuron can either prosper and develop more and more synapses (on the right), or stress can cause a decrease in BDNF production, and vulnerable neurons in the hippocampus can atrophy and possibly undergo apoptosis because this neurotrophic factor is cut off (on the left). These events in turn lead to depression and to the consequences of repeated depressive episodes, namely more and more episodes and less and less responsiveness to treatment. This hypothesis may explain why hippocampal neurons seem to be decreased in size and impaired in function during depression as shown in recent clinical neuroimaging studies.

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