For many years, research on mood disorders has focused on neurotransmitters, particularly on the monoamines (serotonin, norepinephrine, and dopamine) and their action at the neuronal junction, or synapse. Although the monoamine theory helps explain the action of tricyclics, monoamine oxidase inhibitors, and SSRIs, it fails to account for many other things.

Most important, antidepressants do not work as quickly or as effectively as the original monoamine hypothesis would suggest. Monoamine action also does not explain much of the clinical activity of diverse mood stabilizers (lithium [Eskalith, Lithobid], valproic acid [Depakote, Depakene], carbamazepine [Carbatrol, Tegretol]), and some atypical antipsychotics. In addition, the monoamine theory fails to account for recent evidence concerning structural changes within the brain that are associated with affective illness in both humans and animal models.

A more recent conceptualization of mood disorders and their treatment invokes the phenomenon of human brain plasticity, in which the brain is capable of adapting to many circumstances—both external (ie, environmental) and internal (ie, hormones, neurotransmitters, and neurotrophic growth factors). The constant remodeling of the brain is probably responsible for memory formation and the ability to learn motor programs, as well as complex behavioral strategies. A well-known finding that suggested such brain restructuring was that London taxi drivers had larger gray matter volumes in their brains' posterior hippocampi than age-matched controls; this correlated positively with time spent driving a taxi. Brain complexity and adaptability also allows for things to go wrong, which sometimes can result in a mood disorder. **CHANGES IN BRAIN ANATOMY**

Human imaging studies show that major depression correlates with decreased hippocampal volume. The magnitude of the change in hippocampal volume is directly proportional to the length of illness. Up to a 19% loss in hippocampal volume may occur in patients with severe, untreated depression. Such hippocampal changes may explain the memory impairment that is seen in patients with severe depression (the hippocampus has long been known to be important in intact memory function and emotional processing). In addition, the hippocampus has a role in hypothalamic-pituitary-adrenal axis functioning, which is often impaired in patients with severe major depression.

Animal studies have suggested that anatomical changes in the adult hippocampus may result from atrophy of neurons and a reduction of neurogenesis. Chronically exposing rodents to physical stress or exposing primates to psychological stress causes atrophy of carbonic anhydrase 3 pyramidal neurons in the hippocampus that is partly mediated by excessive levels of glucocorticoids. However, the results of postmortem studies in humans with depression have been less clear. Most cellular and morphological postmortem studies in humans with depression have focused on cortical brain structures, where there have been some reported reductions in the size of neuronal cell bodies and number of glia. Anatomical studies of the human hippocampus are scarce, although 1 study of postmortem findings collected from 19 patients with major depression compared with 21 control subjects found that the average soma size of pyramidal neurons was significantly reduced in the major depression group.

Imaging studies from patients who have bipolar disorder also demonstrate significant brain volume reductions, but with considerable variability among studies. Some investigators have reported decreased volume in medial temporal lobe structures, with a greater effect on the amygdala (15.6%) than on the hippocampus (5.3%). Others have found decreases in subgenual prefrontal cortex volume or in the corpus collosum. Antidepressant medications seem able to regrow the hippocampus, in part by stimulating the production of new neurons in the hippocampus from stem cells that reside there. These findings are consistent with the slow clinical action of antidepressants, which usually does not begin for 1 to 2
weeks and can take up to 8 weeks for full effect.

The question then arises of how depression or severe stress might decrease neuronal size and numbers, and how treatment may reverse that atrophy and possibly result in neurogenesis. Research is focusing on the downstream effects of mood stabilizers and antidepressants, including the modulation of intracellular signaling, gene expression, and neural plasticity. Signaling seems to serve to maintain the pathways. Molecular and cellular dysfunction, either because of signaling problems or other issues, might result in destabilization of mood and the associated neurovegetative abnormalities observed in unipolar and bipolar affective disorders.13

### NEUROTRANSMISSION

Neurotransmission begins when "first messenger" neurotransmitters (e.g., monoamines, such as serotonin, norepinephrine, and dopamine, or other transmitters, such as acetylcholine and glutamate) are released from a presynaptic terminal. The neurotransmitter then binds to and activates postsynaptic receptors that modify properties of the postsynaptic cell. These postsynaptic receptors are large protein molecules that are embedded in the lipid neuronal membrane on the receiving neuron's surface. For most monoamines, these receptors are in the guanine-protein-coupled receptor family (which are sometimes called "metabotropic" receptors as opposed to the other main family of receptors called "ion channel" receptors). **G-protein receptors**

When a guanine-protein (G-protein) receptor is occupied by its specific neurotransmitter, it changes shape and releases a G-protein.14 This G-protein second messenger system, in turn, activates enzymes in the neuronal cytoplasm (particularly protein kinases), which add phosphate groups to a variety of proteins within the receiving neuron and set in motion a complex molecular cascade that ultimately turns on genes and DNA in the receiving neuron. Phosphorylation is key to second messenger system function. **Other second messengers**

There are two related second messenger systems that seem particularly important. The first is the phosphoinositol system, which helps regulate the level of calcium in the cytoplasm of neurons (which is very low).

In contrast, calcium is present in high concentrations in seawater and in our bloodstream. That is not mere coincidence, since it represents an attempt at maintaining the mechanisms that worked in the ocean environment before animals transitioned to land. Yet, intracellular levels of calcium are low—0.0001 of that outside the cell. Careful regulation of calcium levels may be required for nature to use phosphorylation as an efficient way to regulate intracellular activities, since very high levels of calcium would cause calcium phosphate to form, interfering with the enzymatic action needed to add or cleave off phosphate groups.15

Another messenger system that works with G-proteins is the adenylyl cyclase, or cyclic adenosine monophosphate (cAMP), second messenger system. The cAMP response element binding (CREB) protein is a transcription factor that can mediate the actions of the cAMP system, again primarily through phosphorylation. Protein kinases are known to phosphorylate and activate CREB proteins. All this is important, since the cAMP cascade and CREB protein may represent the pathway by which serotonin and norepinephrine antidepressants do their work.16

Interestingly, cAMP and other second messengers are not unique to the human brain. Indeed, such small molecules are present in all types of cells, such as fat, muscle, and lymphocytes. In these other cells, the primary messengers may be hormones rather than neurotransmitters.

Even fairly primitive life-forms (e.g., snails and ascaris worms) have cells that function in similar ways, using first and second messengers for signaling between neurons and then across the synapse and into the receiving neuron and its nucleus. This biochemical signaling system seems to be one major mechanism by which nature arranges for cells to work together and is clearly not unique to the human nervous system. **NEUROGENESIS**

The downstream effects of activated G-proteins and other second messengers are relatively slow and prolonged and can take days to weeks for full effect. Virtually any biochemical change in and around the receiving brain neuron is possible. When the volume of messages or the process otherwise becomes abnormal, hippocampal neurons begin to atrophy and other changes may occur. On the other hand, stabilization of brain circuitry is also possible, resulting in corrective gene expression and even neurogenesis.

Medications or other methods of normalizing brain circuitry seem to involve RNA production by activated genes of neurotrophins, particularly brain-derived neurotrophic factor (BDNF), a protein that controls a variety of important neural activities that range from cell differentiation during brain development to cell survival in the mature brain.17

BDNF expression is increased by the excitatory transmitter glutamate and is decreased by the inhibitory transmitter g-aminobutyric acid. Depression and stress decrease BDNF (in animal models), whereas all types of antidepressants and electroconvulsive therapy are known to increase it.
(especially in the hippocampus).  In addition, infusions of BDNF into either the midbrain or hippocampus produce an antidepressant-like effect in behavioral models of depression.  BDNF is also reported to be more prevalent in postmortem tissue of patients who were receiving antidepressant treatment at the time of death.  About 10 years ago, Duman and colleagues clearly stated the hypothesis that BDNF-induced neuronal sprouting in the hippocampus and cerebral cortex could improve synaptic connectivity and function of neural circuits involved in mood regulation. Furthermore, stress-induced vulnerability and the therapeutic action of antidepressant treatments occur via intracellular mechanisms that decrease or increase, respectively, neurotrophic factors that are necessary for the survival and function of particular neurons. This hypothesis not only tries to explain how stress and other types of neuronal insults can lead to depression in vulnerable individuals but also suggests novel targets for the rational design of fundamentally new therapeutic agents. **NEW CLASSES OF THERAPEUTIC AGENTS**

Whereas the BDNF hypothesis predicts that agents directly promoting BDNF function might be as clinically effective as antidepressants, currently no such compounds are available. Perhaps targeting the small molecules that regulate BDNF or other neurotrophic factors might prove useful. This has led investigators back to CREB proteins and the cAMP second messenger system. The BDNF gene is induced in vitro and in vivo by CREB proteins. Virtually all antidepressants increase levels of CREB protein expression and function in several brain regions, including the hippocampus. Inhibitors of phosphodiesterases (PDEs), the enzymes that degrade cAMP also raise levels of CREB proteins; this drug strategy is being pursued. For example, rolipram, a phosphodiesterase 4 inhibitor, shows some antidepressant effectiveness, although it has too many adverse effects (emesis, sedation) for use in humans.

A variety of other clinical and experimental findings seem to support the hypothesis that dysfunction of the system controlling neuronal plasticity or remodeling contributes to the pathophysiology of mood disorders. For example, a recent study that used high-resolution MRI found greater cortical gray matter density in lithium-treated patients with bipolar disorder than in controls, whereas previous studies in untreated patients with bipolar disorder showed decreases of gray matter density in the same anterior limbic areas. Studies of patients with bipolar disorder also show abnormalities in intracellular signal transduction (ie, second messenger systems). These include alterations in cAMP and another second messenger system involving protein kinase C signaling and the phosphatidylinositol pathway. In addition, intracellular calcium signaling systems, which are important in intracellular second messenger systems, showed differences in patients with bipolar disorder versus controls. It also has been shown that serotonin-induced intraplatelet calcium mobilization is enhanced in bipolar disorder. Other studies suggest that the intracellular calcium signaling system is a common mechanism by which diverse mood stabilizer medications (eg, lithium, valproic acid, carbamazepine) may work in bipolar disorder. That a mood stabilizer's therapeutic effects (such as an antidepressant medication's effects) are often slow fits nicely with this model of their impact on second messengers, transcription factors, gene expression, and BDNF-mediated neuronal stabilization.

In practical terms, the importance and ubiquity of second messenger systems, including PDEs, means that they are associated with a wide variety of diseases (not just affective illnesses). PDEs are being actively investigated for use in dementia and other memory disorders. Specific PDE inhibitors (such as rolipram) are being actively studied for their activity in immunomodulation—researchers are looking for impact on autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus, Crohn disease, and ulcerative colitis. Because of their involvement with inflammatory and immunomodulatory responses, asthma and chronic obstructive pulmonary disease are also being investigated. There is even a recent report that demonstrated some potential for rolipram as an antipsychotic agent.

**GENETIC STUDIES**

Further confirmation of the neurogenic hypothesis may come directly from genetic studies. Gene variations encountered in DNA samples of groups of affectively ill patients are being reproduced in genetic knockout mice. Using special techniques, molecular biologists create similar abnormalities in mice by introducing or removing a specific gene variation into a mouse's genome. The effects on overall animal behavior, hippocampal architecture, monoamine production, synaptic transmission, second messengers, cAMP, intracellular calcium, protein kinase, BDNF, and so on are then compared with behavior, brain architecture, and biochemical findings in control, "wild type" mice. Some caution must accompany this type of investigation, since depression is a complex phenomenon in which many genes may be involved. Nongenetic factors are likely to be involved as well, including psychological factors (eg, chronic stress, interpersonal loss, bereavement, blows to self-esteem) or medical disorders (eg, thyroid or adrenal abnormalities, diabetes, collagen disorders,
Parkinson disease). Specifically, it is known from epidemiological studies that only 30% to 50% of the risk for depression is genetic.\(^{34,35}\) It is also not clear whether it makes sense to completely separate out unipolar major depressive disorder from a bipolar affective illness. The 2 disorders have some familial relationship, since rates of major depressive disorder are elevated in relatives of patients with bipolar disorder. However, they are not the same condition, and twin studies of patients with bipolar disorder show greater likelihood of bipolar disorder than unipolar disorder in the other twin.

Another type of genetic study begins with a known neurotrophin, such as BDNF, and looks toward identification of the spectrum of genes associated with its effects on synaptic plasticity.\(^ {36}\) These studies start with an analysis of cell cultures of hippocampal neurons and look for increased expression of various genes within minutes and hours of adding BDNF. In addition, BDNF-induced gene transcripts also may be followed with in vivo animal studies. In recent studies, the loss of BDNF in genetically modified mice seemed to attenuate antidepressant efficacy, providing further support for the neurotrophin hypothesis of depression.\(^ {37}\) There is also preliminary evidence that BDNF polymorphisms or mutations are associated with human mood disorders.\(^ {38}\) Obviously, many other genetic approaches are possible. Linking genes to second messengers, neurotrophins, changing brain architecture and function, and behavior and affect is not simple, but progress is likely.

**CONCLUSION**

Of necessity, what I have outlined is sketchy and oversimplified. However, there is much new evidence from multiple investigations and approaches in humans and animals to suggest that the effectiveness of SSRIs and other antidepressants (as well as mood stabilizers) lies not just with direct effects on synaptic transmission, but (more important) with what happens intracellularly in receiving neurons. Evidence is accumulating that complex effects within neurons exposed to amplified signaling affect the receiving neuron's nucleus and DNA. Genes are turned on, leading to adaptive changes, including neurogenesis, and synaptic growth leading to beneficial changes within important brain areas, such as the hippocampus.

Understanding affective illness as a brain problem (although one influenced by stress and other environmental impacts) will very likely result in new treatments. These will probably include new medications that use novel mechanisms of action that will enhance the functioning of an adaptable and ever-changing brain.

**References:**


