NEUROSCIENCE:

A New Molecule to Brighten the Mood

Depression is a mood continuum, ranging from normal but temporary "bad days" to a completely disabling clinical condition characterized by overwhelming despair that lasts for weeks or months. A popular theory is that a breakdown in signaling by the brain neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is critically involved in the symptoms of clinical depression, but the nature of this defect has proved elusive. The study by Svenningsson et al. on page 77 of this issue (1) identifies a powerful interaction between a brain protein called p11 and a serotonin receptor (5-HT1B subtype) that has been previously associated with mood regulation. Moreover, in a clever set of experiments using human brain and sophisticated animal models, the authors show that a deficit of p11 is linked to depression, whereas an increase in p11 is linked to the relief of depression. Overall, this finding represents compelling evidence that p11 has a pivotal role in both the cause of depression and perhaps its successful treatment.

The 5-HT1B receptor is one of 14 serotonin receptor subtypes and is abundant in the brain across a range of species (2). The rodent 5-HT1B receptor is well suited for investigation because it is remarkably similar in structure, functional characteristics, and distribution to the human homolog. Recent studies using newly available ligands for the 5-HT1B receptor and genetically altered mice with the 5-HT1B receptor "knocked out" have firmly linked this receptor to an extraordinarily diverse range of physiological functions and behaviors including not only mood but also cognition, aggression, addiction, sleep, and feeding (3).

To produce this range of effects, the 5-HT1B receptor must be transported to the terminal membranes of both serotonin- and nonserotonin-containing neurons, where it signals by coupling to intracellular heterotrimeric GTP-binding proteins (G proteins). Unraveling this trafficking process presents a major challenge, however, because recent discoveries for other G protein-coupled receptors suggest the involvement of complex networks of interacting proteins, which may number several dozen (4).

Using yeast two-hybrid screening, Svenningsson et al. identify p11 as the first known protein-binding partner of the 5-HT1B receptor. p11, which is a member of the S100 family of proteins that translocate their binding partners to the plasma membrane (5), was shown to have a distribution in the mouse brain that overlaps that of the 5-HT1B receptor. Using simple cell culture systems, Svenningsson et al. convincingly show that p11 makes more 5-HT1B receptors available at the cell surface, thereby increasing 5-HT1B receptor signaling efficacy, while leaving the dynamics of other G protein-coupled receptors untangled.
unchanged. The discovery of p11 now invites investigation of the myriad other interacting proteins that are likely to be critical to 5-HT\textsubscript{1B} receptor function.

Interestingly, Svenningsson et al. found decreased p11 expression in postmortem brains of depressed patients, and also in a well-validated genetic mouse model that displays many of the behavioral and physiological symptoms of clinical depression (6). Crucially, p11 knockout mice exhibited increased depression-like behavior, whereas genetically altered mice that overexpress p11 showed the opposite behavior. These observations provide a convincing association between p11 expression and depression-like behaviors in animals (see the figure), and suggest that a deficit in p11 expression is linked to depressive illness in patients. If the postmortem p11 data are replicated in larger populations of depressed patients, this would be a major breakthrough in our molecular and genetic understanding of depression.

What might cause a deficit in p11 expression in depression? Evidence that other serotonin-related gene products (including tryptophan hydroxylase, 5-HT\textsubscript{1A} receptors, and the serotonin transporter) are abnormal in depression (7) suggests that a generalized dysfunction of serotonin neurons, possibly of developmental origin, may be responsible. However, the different anatomical localizations of some of these gene products might argue for more than one underlying pathophysiological mechanism. On the other hand, depression is often associated with stressful life events and an ensuing excess of glucocorticoid hormones, which can have striking effects on the serotonin system at many levels (8). Because the expression of p11 and other members of the S100 family is sensitive to glucocorticoids (9), stress may be a factor in the p11 changes.
The past decade has seen the evolution of a fascinating theory to explain the antidepressant effect of drugs like Prozac that act to inhibit the reuptake of serotonin by neurons. This theory posits that elevated serotonin levels trigger signaling cascades that activate gene programs to enhance neuronal survival and connectivity—the latter having failed because of the adverse effects of stress and other environmental factors (10).

Although this line of thought is driving promising pharmacological strategies for improved antidepressant therapies, our knowledge of the key molecules that are changed by antidepressants to bring about the relief of the symptoms of depression is far from complete.

Intriguingly, Svenningsson et al. found that administration of different antidepressants to mice increased p11 expression. In addition, antidepressant-induced behavioral effects in mice were replicated by p11 overexpression and attenuated by genetic removal of p11. These observations pinpoint increased p11 expression as a crucial event in the cascade of molecular changes leading up to the behavioral effects of antidepressant treatment.

Because of the strong p11-5-HT\textsubscript{1B} receptor interaction, it is tempting to suggest that altered 5-HT\textsubscript{1B} receptor signaling is the cause of the behavioral changes induced by genetic manipulation of p11 expression. Indeed, Svenningsson et al. show that the behavioral effects in mice induced by changes in p11 expression are accompanied by parallel changes in 5-HT\textsubscript{1B} receptor expression. However, this notion should be interpreted with caution. p11 also mediates trafficking of certain cation channels (11, 12).
and changes in this function of p11 might influence mood, although presently this link is tenuous. In addition, unlike p11 deficits, pharmacological or genetic interventions that attenuate 5-HT$_{1B}$ receptor signaling do not evoke overt signs of behavioral depression in animals (13, 14). However, such interventions may not accurately model the effects of p11 deficiency.

Despite these caveats, there is tantalizing evidence of reduced 5-HT$_{1B}$ receptor function in depressed patients (15, 16) that might profit from further investigation. For instance, novel compounds are being developed to image 5-HT$_{1B}$ receptors in living humans (17). Moreover, there are reports that triptan drugs with 5-HT$_{1B}$ agonist properties, which are widely used in the treatment of migraine, have antidepressant effects in patients and that more selective agonists with better brain penetrability are antidepressant in animal models (18-20).

The cause of depression and the relief of its symptoms are likely to be influenced by many different genes. The list of candidate genes linked to the function and effects of serotonin now grows, not just through the addition of p11, but also the large number of serotonin receptor-interacting proteins that p11 represents. The case for p11 as a key molecule in mood regulation is convincing, and it is now timely for translational science to take this exciting development to the next step.

References
2. N. M. Barnes, T. Sharp, Neuropharmacology 38, 1083 (1999) [Medline].
11. C. Girard et al., EMBO J. 21, 4439 (2002) [Medline].