DEPRESSION

p11 and Gene Therapy for Severe Psychiatric Disorders: A Practical Goal?

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In this issue of *Science Translational Medicine*, Alexander and colleagues describe coherent evidence drawn from humans and from modeled animals that supports a brain region–specific gene therapy for depression: adeno-associated virus (AAV)–mediated transfer of the gene encoding p11 to the nucleus accumbens (NAcc). The investigators found that focal NAcc knockdown of p11 expression in mice resulted in behavioral deficits related to depression and that AAV-mediated p11 gene transfer to the NAcc rescued the depression-related behavioral deficits of mice in which endogenous p11 had been genetically knocked out. They also found that p11 levels were lower in the NAcc of patients with depression than in the NAcc of matched controls. Taken together, the data suggest that gene therapies aimed at enhancing p11 in the NAcc may represent promising new approaches for treating depression; however, a large number of clinical and regulatory issues must be overcome before such therapies can be implemented.

Major depressive disorder (MDD) is a common, chronic, severe, and often life-threatening illness. It is a leading cause of disability worldwide (*1*–*4*). MDD leads to limited functioning, which often results in decreased productivity in patients' personal and professional lives. The prognosis for a substantial subset of MDD patients is often poor, as the illness is associated with high rates of relapse, lingering residual symptoms, functional impairment, and diminished well-being. In this issue of *Science Translational Medicine*, Alexander and colleagues report a major preclinical advance in the treatment of this disorder (*5*).

Most investigators agree that MDD is a multifactorial disease stemming from a combination of genetic factors—including sequence variations in assorted protective/preventive genes and susceptibility/risk genes—as well as environmental influences such as chronic stressors and traumatic experiences that can exacerbate an underlying susceptibility. Historically, the brain systems receiving the greatest attention in neurobiological studies of mood disorders were the monoamine neurotransmitter systems (involving, for example, serotonin, norepinephrine, and dopamine). These systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits and are thought to support the mood, thought, behavioral, and visceral manifestations of mood disorders. For example, the widely prescribed selective serotonin reuptake inhibitor (SSRI) antidepressants were designed to affect the uptake of serotonin at synapses. Currently, however, there is a growing consensus that MDD does not simply result from a neurotransmitter imbalance; rather, this disorder is thought to arise from aberrant synaptic and neural plasticity in critical circuits mediating affective, cognitive, and motoric function. The remarkable plasticity of neuronal circuits is achieved through different biological means, including alterations in gene transcription and intracellular signaling cascades. These changes modify diverse neuronal properties such as neurotransmitter release, synaptic function, and even the morphological characteristics of neurons.

Although depression is treatable, the effectiveness and delayed onset-of-action profile (often several weeks) of current antidepressants—as well as the adverse effects associated with their use—remain far from acceptable (*6*). For instance, data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that the SSRI citalopram was associated with a remission rate of only 36.8% and an intolerance rate of 16% (*7*). Data from the STAR*D study further showed that roughly 40% of patients with depression relapsed within 1 year (*7*). Despite the fact that MDD is increasingly recognized as a major health problem, recent decades have been marked by a dearth of new treatments (*8*), and there is a clear need to develop improved therapeutics, particularly for patients refractory to existing treatments. The first antidepressants were developed in the late 1950s and 1960s and are believed to exert their initial effects by increasing synaptic monoamine concentrations; although they have a better tolerability profile, the newer antidepressants developed in the past two decades have similar mechanisms as the first-generation ones (*1*–*4*, *9*).

Developing new treatments for depression has long been constrained by our incomplete understanding of the molecular pathophysiology of depression and of the downstream molecular and cellular therapeutic mechanisms of existing antidepressants (*1*–*3*, *9*). However, recent preclinical studies have discovered several promising mood modulators, including (i) receptors for the excitatory neurotransmitter glutamate; (ii) brain-derived neurotrophic factor (BDNF), a protein that modulates neuronal survival and growth as well as synaptic plasticity; (iii) cyclic adenosine monophosphate (cAMP) response element–binding (CREB), a transcription factor that regulates the expression of genes such as *BDNF*; (iv) deltaFosB, a transcription factor that has been linked to increased BDNF and other proteins; and (v) mammalian target of ra-

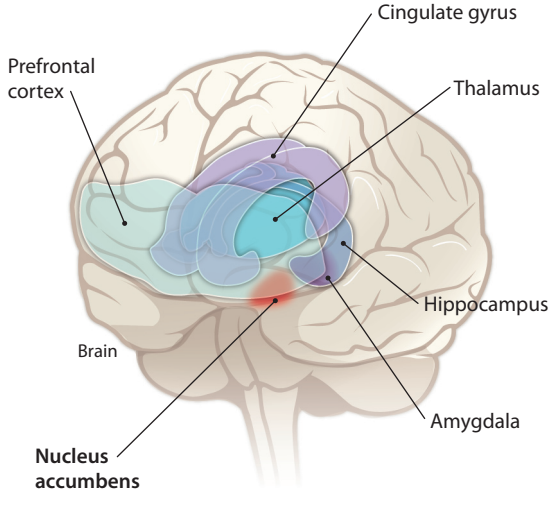

Fig. 1. Key brain regions. Both human and preclinical data support the involvement of these brain regions—including the nucleus accumbens—in depression and reward mechanisms.

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pamycin (mTOR), a kinase involved in synaptogenesis (*1*–*4*, *10*, *11*). Interestingly, some promising modulators such as CREB and BDNF produce opposing behavioral effects in different brain regions (*4*). Therefore, manipulating extra- and intracellular targets in a brain region–specific manner will clearly be an important issue in developing new therapies for depression.

Toward this end, Alexander and colleagues (*5*) describe coherent evidence drawn from humans and from modeled animals that supports a brain region–specific gene therapy for depression: adeno-associated virus (AAV)–mediated transfer of the gene encoding p11—a protein that binds certain serotonin receptors—to the nucleus accumbens (NAcc), a brain region associated with reward and pleasure-seeking behaviors (Fig. 1). In this carefully constructed study, the investigators found that focal NAcc knockdown of p11 expression in mice resulted in behavioral deficits related to depression and that AAV-mediated gene transfer to the NAcc rescued the depression-related behavioral deficits of mice in which endogenous p11 had been genetically knocked out (p11 knockout mice). They also found that p11 levels were lower in the NAcc of patients with depression than in the NAcc of matched controls. Taken together, the data suggest that gene therapies aimed at enhancing p11 in the NAcc may represent promising new approaches for treating depression.

SSRIs are clinically effective agents for the treatment of depression, although as noted above, their efficacy is far from ideal. The therapeutic mechanism of SSRIs downstream to serotonergic increases in the synapse remains largely unknown. Several classes of serotonin receptors are differentially distributed in the brain and on post- and presynaptic sides of a synapse. As with other neurotransmitter receptors, these receptors must be on the cell surface in order to receive extracellular stimulation by serotonin. Several years ago, Svenningsson and colleagues launched a study aimed at identifying intracellular molecules that interact with serotonin receptors and that mediate the cellular and behavioral functions of those serotonin receptors related to depression (*12*). Cell-surface receptors use a variety of membrane-transducing mechanisms to transform an agonist's message into cellular responses. In neuronal systems, the most typical responses ultimately involve changes in transmembrane voltage and, hence, neuronal changes in excitability; such changes may occur slowly or rapidly. Many receptors in the central nervous system (particularly for monoamine neurotransmitters) do not have intrinsic ionic conductance channels within their structure but instead regulate cellular activity by coupling to G proteins, thus generating various second messengers. The complex mechanism by which extracellular signals are translated into cellular changes involves at least three principal modes of regulation: desensitization, down-regulation, and trafficking (*13*). Receptor trafficking is a mechanism that brings receptors into contact with different effector systems (including nuclear effector systems) and is believed to underlie various forms of neuroplasticity (*13*).

The p11 protein, also known as S100A10, is a member of the S100 calcium effector protein family (*14*); however, p11 is insensitive to calcium because of peptide sequence differences in the EF-hand calcium-binding motif (*14*). p11 is known to be involved in the trafficking of its interacting proteins to endosomes—membrane-bound compartments that function in endocytosis—and to the cell surface (*14*). Using the yeast two-hybrid screen, Svenningsson and colleagues demonstrated that the 5HT1B serotonin receptor interacted with p11 (whereas the 5HT1A, 5HT2A, 5HT5A, and 5HT-6 serotonin receptors and the D1 and D2 dopamine receptors did not) (*12*). Follow-up experiments showed that p11 enhanced the appearance of 5HT1B on the cell surface and that this p11-mediated surface localization of 5HT1B correlated with the enhanced inhibitory effect of 5HT1B stimulation on cAMP accumulation (*12*). p11 is also critical for the inhibition of corticoaccumbal glutamatergic synaptic transmission (that is, synaptic neurotransmission of glutamatergic neurons originating from the cerebral cortex to the NAcc) by serotonin and for the down-regulation of extracellular signal–regulated kinase (ERK) and phosphorylation of synapsin I—a protein on the cytoplasmic surface of synaptic vesicles—by serotonin and anpirtoline (a 5HT1B receptor agonist) (*12*). These data indicate that p11 is essential for 5HT1B receptor–mediated intracellular signaling and neuronal function.

In the same study, the investigators also found that repeated treatment with imipramine (a classic tricyclic antidepressant) for 14 days or electroconvulsive treatment (ECT) for 10 days increased p11 mRNA and protein levels in the forebrain of naïve animals (*12*). Specifically, forebrain p11 mRNA and protein levels were lower in helpless H/Rouen mice—a genetic model of depression—than in nonhelpless NH/Rouen mice (*12*). Furthermore, the investigators found that transgenic mice overexpressing p11 displayed less immobility time in the tail suspension test (a widely used paradigm for assessing mood-related behaviors in rodents), an effect traditionally associated with antidepressant treatment (*12*). Conversely, p11 knockout mice displayed increased immobility time in the tail suspension test. The p11 knockout mice also displayed reduced consumption of a palatable 2% sucrose solution, but not water, in a paradigm assessing behavioral deficits associated with anhedonia (*12*), which is loosely defined as an impaired capacity to experience or anticipate pleasure and is a key symptom of depression in humans. p11 mRNA and protein concentrations were also found to be reduced in the anterior cingulate cortex (Fig. 1) of patients with depression (*12*). This work by Svenningsson and colleagues (*12*) was the first to suggest that p11 plays an essential role in intracellular signaling initiated by 5HT1B receptor stimulation by serotonin, serotonin-modulated neuronal circuitry, behaviors related to depression, and ultimately the molecular pathology of depression (Fig. 2).

In a later study, these same investigators demonstrated that p11 also enhanced the localization of 5HT4 receptors at the cell surface and that 5HT4 receptor stimulation induced cAMP production and ERK phosphorylation (*15*). p11 is also necessary for facilitating the ability of RS67333, a 5HT4 receptor partial agonist, to reduce immobility in both the tail suspension and forced swim tests (*15*). With respect to human studies, Anisman and colleagues noted in a small cohort of samples that p11 mRNA levels were lower in the frontopolar cortex, orbitofrontal cortex, hippocampus, and amygdala, but not in the paraventricular nucleus, of suicide victims as compared to controls (*16*). These data further support the critical role of p11 in regulating behaviors related to depression.

Up-regulation of BDNF is a common effect of diverse antidepressants as well as ECT and mood stabilizers (*4*, *17*). Meta-analyses have shown that in depressed patients, BDNF serum concentrations are positively correlated with antidepressant response. In rodents, direct infusion of BDNF into the midbrain, the dentate gyrus of the hippocampus, or the lateral ventricle produces antidepressant-like effects in im-

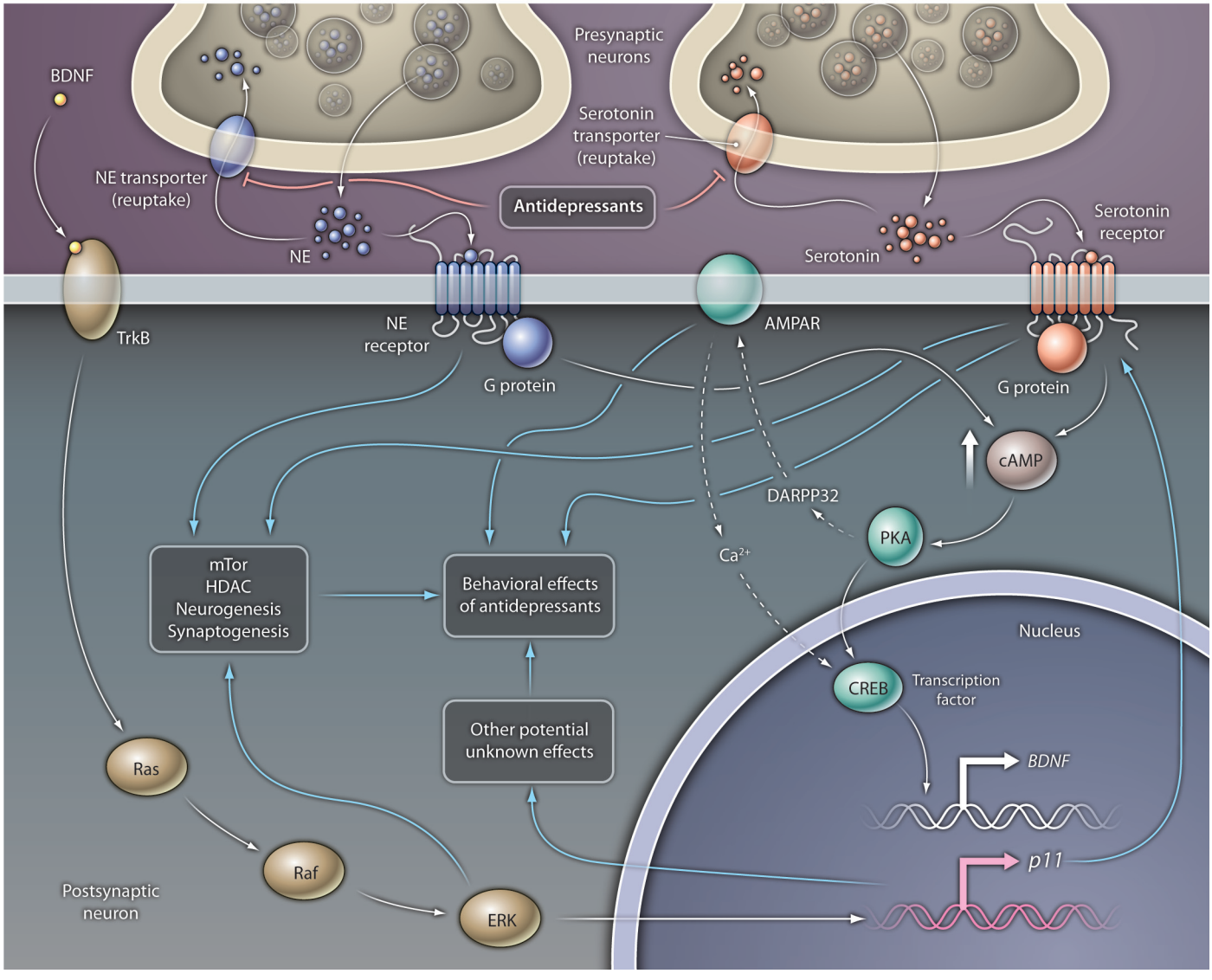

Fig. 2. The role of p11. Putative sequential molecular events involving the action of antidepressants and p11 overexpression in experimental models of depression. Antidepressants increase synaptic monoamine levels by inhibiting monoamine reuptake or breakdown. Monoamines stimulate intracellular cAMP production through their G protein–coupled receptors, and cAMP activates protein kinase A (PKA). PKA directly and indirectly [through potentiation of the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR)] activates the transcription factor CREB, which in turn increases BDNF expression. BDNF activates TrkB, its cell surface receptor, and through TrkB activates the intracellular ERK pathway. Through unknown molecular steps, ERK increases p11 expression. p11 enhances cell-surface localization of 5HT1B and 5HT4 serotonin receptors. Via its effects on serotonin receptors and other potential targets, p11 affects behaviors related to depression. Antidepressants may also produce behavioral effects through other known molecular and cellular actions, such as mTOR up-regulation, histone deacetylase (HDAC) modulation, synaptogenesis, and neurogenesis, which can complement those mediated through p11. NE, norepinephrine; DARPP32, dopamine- and cAMP-regulated phosphoprotein.

mobility tests or in the learned helplessness paradigm of depression (*18*–*20*). Very recently, Warner-Schmidt and colleagues demonstrated that the effects of lateral ventricle BDNF infusion on immobility in both the tail suspension and forced swim tests were absent in p11 knockout mice (*21*). Furthermore, p11 is known to dramatically enhance tissue plasminogen activator (tPA) activity (*22*). This finding is particularly notable because a large proportion of neuronal BDNF is secreted in the pro-form, which is subsequently converted to mature BDNF (mBDNF) by extracellular proteases such as plasmin or matrix metalloproteinases (*23*). tPA, an extracellular protease that converts the inactive zymogen plasminogen to plasmin, is of particular interest because of its ability, via plasmin activation, to convert proBDNF to mBDNF in the hippocampus; this conversion is required for late-phase long-term potentiation, which is one of the processes underlying synaptic plasticity (*23*).

The paper by Alexander and colleagues (*5*) expands this work by revealing the brain region critical to the action of p11 on behaviors related to depression. The authors studied two regions: the anterior cingulate cortex and the NAcc. AAV vectors delivered small interfering RNA for knockdown of endoge-

nous p11 mRNA or p11 cDNA for p11 overexpression. Focal knockdown of p11 in the NAcc increased immobility time in the tail suspension and forced swim tests in otherwise normal adult C57B1/6 mice. However, knockdown in the anterior cingulate cortex did not affect immobility measures. The authors further tested whether AAV-mediated p11 expression rescued depression-related behavioral deficits in p11 knockout mice. They found that p11 focal expression in the NAcc of p11 knockout mice alleviated increased immobility time in the tail suspension test; the same treatment had no significant effect on immobility time in wild-type mice. Furthermore, focal NAcc p11 expression in p11 knockout mice increased their consumption of 2% sucrose solution but not water. Lastly, the investigators found significantly lower p11 protein concentrations in NAcc tissue from depressed patients as compared with controls. Taken together, these data demonstrate that p11 in the NAcc modulates depression-related behaviors. It is also important to note, however, that p11 levels were reduced in the anterior cingulate cortex of patients with depression (*5*), that antidepressants increased p11 levels in the prefrontal cortex (*5*), and that animal studies are by nature unable to directly address issues related to mood and cognitive symptoms in depression; thus, we cannot yet rule out the possible role of a p11 deficit in the anterior cingulate cortex in the overall manifestation (*5*) of depression (*24*).

Why p11 proteins are down-regulated in the brain regions of patients with depression or those who committed suicide is unclear; however, given that mRNA concentrations are also down-regulated, transcriptional and mRNA stability alterations are the logical suspects. To date, few reports suggest that single-nucleotide polymorphisms of the p11 gene might be risk or predictive factors for depression, suicide, or response to antidepressants (*25*, *26*). Current genetic association data are similarly negative. This finding could suggest that dysregulation of p11 expression by other genes or environmental factors is a more likely explanation for the lower mRNA concentrations observed in the brains of depressed patients. Notably, studies have shown that BDNF up-regulates p11 expression through the TrkB and ERK pathways (Fig. 2) (although not through the phosphoinositide 3-kinase pathway, which can also be activated by TrkB) (*21*). It is also worth noting that p11 expression is known to be up-regulated by glucocorticoids—a class of steroid hormones—in peripheral and neuron-like cells (*27*). Furthermore, p11 mRNA concentrations were found to be lower in the postmortem cortical tissue of individuals with posttraumatic stress disorder (PTSD) than controls (*27*). In animal studies, inescapable tail shock—a putative model of PTSD—elevated plasma corticosterone (a glucocorticoid involved in stress response) and p11 concentrations in the prefrontal cortex, hippocampus, and amygdala (*27*). Whether the manner in which BDNF and glucocorticoids regulate p11 also applies to NAcc neurons is unknown.

The NAcc is the key member of the mesolimbic reward circuit, one of the major circuits regulating hedonic activity (*28*). In preclinical studies, manipulating genes encoding such proteins as CREB (*29*), activating transcription factor 2 (a transcription factor related to CREB) (*29*), and TkrB (*30*) in the NAcc altered the results of immobility tests. Clinically, direct stimulation of the NAcc (also known as deep brain stimulation) improved anhedonia measures in depressed patients (*31*) and alleviated depressive symptoms in patients with treatment-resistant depression (*32*). Such evidence suggests that the NAcc is a reasonable choice when developing brain region–specific therapies for depression. As Alexander and colleagues point out, the vector used in this paper is the same one used for developing Parkinson's disease–related (*33*) and late infantile neuronal ceroid lipofuscinosis–related gene therapies (*34*); both have been tested in clinical trials. Although the down-regulation of p11 in the NAcc in depression should be further tested in additional cohorts of postmortem brain tissues, the current data support the further development of AAV vector–mediated p11 gene expression in the NAcc as a putative brain region–specific gene therapy for depression.

Echoing the groundbreaking developments seen in other therapeutic areas—for instance, stem cell, gene, and immuno- (vaccine and antibody) therapies for Parkinson's and Alzheimer's diseases—challenging issues in the development of p11 gene therapy for depression remain to be addressed. The specific issues for depression include the neurobiological and behavioral impact of p11 overexpression in the NAcc after recovery from depression and the potential efficacy of p11 overexpression in the NAcc in patients with treatment-resistant depression. Furthermore, although the new preclinical data reviewed here are compelling, another major question that needs to be addressed concerns whether or not gene therapy can actually be considered a viable therapeutic approach for human psychiatric conditions such as MDD. In this context, it is worth noting the enormous toll that MDD exerts worldwide and the clear and compelling need to develop newer and better therapeutics to treat this devastating illness. The World Health Organization's Global Burden of Disease Study identified MDD as the leading cause of disability in the Western World for those aged 15 to 44 years (*35*). In addition to the disabling nature of the illness, it can also be fatal. For instance, in the United States it is estimated that twice as many individuals die each year from suicide as compared to homicide, that suicide takes far more lives than HIV, and that only three forms of cancer have a higher annual death rate than suicide. As this elegant study by Alexander and colleagues demonstrates, a putative new therapy for depression has emerged from preclinical studies. However, the use of gene therapies to treat complex psychiatric diseases represents uncharted territory. Although we have embarked upon a promising new path, a large number of clinical and regulatory issues must be overcome before such therapies can be implemented (*35*).

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