Models of Antidepressant Action

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Although immediate pharmacologic targets can be identified for most antidepressant treatments, elucidation of the critical biological mechanisms leading to symptom relief has defied decades of research. In this review, selected neurotransmitter, biochemical, and anatomic models of antidepressant action are considered with regard to their explanatory power and therapeutic applicability. Monoamine models have been a focus of research attention on antidepressant action, an appropriate emphasis in that virtually all antidepressant medications have high affinity for monoamine substrates. Furthermore, prevailing monoamine models have suggested some promising therapeutic strategies. Nevertheless, these models are ultimately incomplete and do not fully explain important clinical limitations of current treatment: delayed response, incomplete efficacy, and unsustained remissions. Continued therapeutic advancements will likely require the development of models of antidepressant action that extend beyond the monoamines. *(J Clin Psychiatry 1999;60[suppl 14]:16–20)*

Intensive effort in the development of antidepressant treatments over the last 4 decades has led to the current availability of almost 3 dozen medications worldwide. To date, all of the commonly used agents have specific pharmacologic effects on monoamine systems. Despite immediate and potent binding to monoamine targets, antidepressant medications generally require weeks of administration before optimal antidepressant benefits are achieved. Consideration will be given to the role of serotonin (5-HT) and norepinephrine in the pathophysiology of major depression and in the mechanism of action of antidepressants, focusing on clinical findings. Development of new treatments has traditionally been guided by interpretation of these findings; however, persisting treatment limitations (i.e., delayed onset, "efficacy ceiling," unsustained remissions) reflect limitations of monoamine models of antidepressant action. A sampling of other, potentially complementary, conceptions of antidepressant action is also presented.

SEROTONIN THEORIES OF ANTIDEPRESSANT ACTION

The original serotonin deficiency hypothesis suggested that depression results from decreased central 5-HT and that antidepressants work via increasing 5-HT,[1,2] a hypothesis founded on the observation that monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) both increase 5-HT levels in animals and possess potent antidepressant activity. This model, however, did not explain important findings: (1) the ambiguous relationship of 5-HT and metabolite levels with depressive symptoms, (2) the latency of response to antidepressants, (3) drug combinations that rapidly enhance 5-HT release but do not confer immediate antidepressant effects, and (4) disruption of 5-HT neurotransmissions (via the paradigm of tryptophan depletion[3]) in nondepressed human subjects, as well as in recently remitted patients taking agents other than SSRIs, that does not provoke depressive symptoms.

Several groups later advanced hypotheses of antidepressant action based on enhanced 5-HT neurotransmission[4–6] founded largely on preclinical observations of the effect of repeated antidepressant administration in altering receptor sensitivity, receptor density, neuronal firing characteristics, and behavioral responses to specific serotonergic agents. In these studies, no solitary or universal effect of repeated antidepressant administration emerged; however, considered in entirety, these studies show that chronic—but not acute—antidepressant treatment increases the efficiency of serotonergic neurotransmission.

Electrophysiologic assessment of 5-HT neurons and antidepressant effects on them have refined the prevailing serotonin-based model of antidepressant action.[6,7] Chronic, but not acute, administration of all antidepressants tested to date is associated with enhanced hippocampal 5-HT_{1A}–mediated neurotransmission, as determined via electrophysiologic studies in rodents. The mechanism of this enhancement varies among antidepressant classes. Chronic administration of the tricyclic noradrenergic and mixed reuptake inhibitors, electroconvulsive shocks, and lithium enhances postsynaptic 5-HT_{1A} responsivity with-

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out significantly altering presynaptic 5-HT_{1A} function. Chronic administration of selective serotonin reuptake inhibitors (SSRIs) and MAOIs leads to desensitization of the presynaptic 5-HT_{1A} and, in the case of SSRIs, 5-HT_{1D} autoreceptors. Mirtazapine administration is associated with increased 5-HT neurotransmission via desensitization of α_2-adrenergic receptors located on 5-HT nerve terminals.[8]

Clinical application of this model would suggest that concurrent administration of a 5-HT_{1A} antagonist with an SSRI in depressed subjects may result in immediate remission. Although there are no available selective 5-HT_{1A} antagonists for human use, pindolol, commonly known as a nonselective β-adrenergic blocker, has potent 5-HT_{1A} antagonism activity. In laboratory animals, concurrent administration of pindolol and SSRIs has been shown to increase serotonin release[9] and neuronal firing rate.[10] Multiple open and controlled trials have assessed the use of pindolol in hastening response to SSRIs.[11–17]

Although the initial open-label trials from 2 research groups suggested that over 80% of patients (13/16) respond within 1 week,[12,13] controlled trials have yielded more moderate results. The majority of randomized controlled trials with pindolol-SSRI combinations have reported response rates upward of 50% after 2 weeks on medication. A negative report by our group[11] may be interpreted to suggest that pindolol is differentially effective in select depressed populations, specifically in patients with first-episode depressions characterized by acute onset. Overall, the reported successes of pindolol in hastening antidepressant response add compelling support to the model of SSRI action elucidated above.

Additionally, application of this model would suggest that concurrent administration of an SSRI with an α_2-adrenergic antagonist would accelerate and/or enhance serotonergic neurotransmission by blocking inhibitory α_2-adrenoceptors on 5-HT nerve terminals. Extrapolating clinically, such a pharmacologic strategy may hasten antidepressant response or improve efficacy. In a test of this strategy, our group has found that yohimbine, an α_2-adrenergic antagonist, hastens response to fluoxetine[18] and reduces depression scores in subjects who were resistant to multiple medication trials including an ongoing trial of fluvoxamine.[19] Indeed, these results are consistent with the anecdotal impression among clinicians that mirtazapine addition is efficacious in SSRI-resistant depression.

In sum, a prevailing serotonin model of antidepressant action based largely on electrophysiologic findings has proved useful in predicting pharmacologic strategies that improve the effect of SSRIs, pointing directly toward the potential clinical application of 5-HT_{1A} antagonists (i.e., pindolol) and α_2-adrenergic antagonists (i.e., mirtazapine and yohimbine). Nevertheless, persisting limitations of this model include difficulty in accounting for multiple phenomena: (1) there is continued presence of some latency of response that is observed in pindolol-SSRI combinations even when dosed under optimal circumstances; (2) paradigms that likely enhance 5-HT_{1A}–mediated postsynaptic neurotransmission, such as tryptophan plus MAOI combinations, do not result in rapid antidepressant effects but more consistently symptoms of nausea and involuntary clonic movements[20]; (3) remissions induced by desipramine are not vulnerable to transient reversal by disruption of serotonergic function (via tryptophan depletion), while remissions induced by SSRIs as well as MAOIs are transiently reversed under such conditions. This latter finding casts doubt on the clinical relevance of enhanced serotonergic neurotransmission as a universal, critical feature of all antidepressant classes.

CATECHOLAMINE MECHANISMS OF ANTIDEPRESSANT ACTION

Original catecholamine hypotheses of major depression posited that some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain[21] and that antidepressants work by enhancing catecholamine levels.[21,22] The available evidence included observations that antidepressant agents bound specifically to catecholaminergic targets and that medications which disrupted catecholaminergic function (i.e., reserpine and methyldopa) were associated with the emergence of clinical depression. Criticisms, much analogous to those offered the original serotonin hypotheses of antidepressant action, can be applied here as well.[23,24] For example, disruption of catecholamine function via administration of α-methyl-paratyrosine (a potent inhibitor of the rate limiting step in catecholamine synthesis) does not significantly alter mood in never-depressed control subjects.[25,26] Additionally, depression that responded to SSRI treatment is not transiently reversed by disruption of catecholaminergic function.[27]

Based on preclinical (electrophysiologic and neurochemical) and clinical studies, refined models assert that chronic antidepressant treatment is associated with diminished β-adrenergic–mediated neurotransmission[28] and diminished β-adrenergic receptor sensitivity.[4] Repeated administration of all classes of antidepressant medications to laboratory animals may decrease norepinephrine release, as evidenced by decreased activity of the key enzyme involved in catecholamine synthesis, tyrosine hydroxylase. Furthermore, such medication administration is commonly associated with decreased β-adrenergic receptor binding. Although compelling in the range of evidence, this model has demonstrated limited clinical application. For example, β-adrenergic antagonists (with the exception of pindolol) do not enhance antidepressant activity,[15] and some researchers have even argued that it is associated with an increased incidence of depression in patients treated for hypertension.[29]

Perhaps accounting for these discrepant phenomena, Duman and colleagues[30] have suggested that chronic antidepressant treatment results in enhanced "neurotransmission" as mediated by specific intracellular signaling mechanisms (i.e., increased levels of cyclic adenosine monophosphate [cAMP]). In this model, subsensitization of β-adrenoceptors may represent a homeostatic response to enhanced synaptic norepinephrine levels. In support of this model, clinical trials have demonstrated that agents which increase cAMP levels (i.e., phosphodiesterase inhibitors such as rolipram and papaverine) possess antidepressant activity.[31,32]

Overall, catecholamine and serotonin hypotheses of antidepressant action are ultimately incomplete. Monoaminergic-related antidepressant medications may exert antidepressant properties via another, as yet unidentified, downstream or intracellular system that may be highly regulated by monoamines.

NMDA MODEL OF ANTIDEPRESSANT ACTIVITY

Although little direct evidence suggests that excitatory amino acids, such as glutamate, are involved in the pathophysiology of major depression, a growing literature suggests the role of excretory amino acids in the mechanism of antidepressant action. Multiple types of *N*-methyl-D-aspartate (NMDA) antagonists have been demonstrated to be effective in animal models of depression and in models predictive of antidepressant action.[33] In clinical investigations, the administration of NMDA antagonists to nondepressed subjects has been associated with mild euphoria.[34] Chronic, but not acute, administration of virtually all antidepressant medications has been shown to evoke specific adaptations in NMDA receptors. These adaptations were observed in 22 of 23 antidepressants tested, but not in other types of psychotropic agents.[35] Thus, this marker has proved to be a more robust predictor of antidepressant response than either the forced-swim test or cortical β-adrenoceptor density down-regulation. Although there is a lack of selective and suitable NMDA antagonists available for clinical use, limited therapeutic studies support an NMDA-mediated model of antidepressant action. Preliminary evidence from our group demonstrates that subanesthetic doses of ketamine rapidly reduce symptoms in unmedicated depressed patients. Strong preclinical support and intriguing preliminary trials justify further work in the development of selective NMDA antagonists as antidepressants.

NEUROPEPTIDE ANTAGONISTS IN ANTIDEPRESSANT ACTION

Neuropeptides have long been identified as having neurotransmitter-like and modulatory actions; however, a clear understanding of their physiologic role in psychiatric diseases has remained elusive. For example, substance P, the first described neuropeptide,[36] has not figured significantly in affective disorders research. Based on empirical observations, a substance P antagonist was observed to have antidepressant activity and was subsequently tested in depressed populations. Surprisingly, a substance P antagonist has recently been demonstrated to have comparable antidepressant efficacy to paroxetine, with both agents testing superior to placebo.[37] In preclinical models, this agent was not associated with monoaminergic activities that are commonly found with virtually all approved antidepressant medications. This serendipitous finding may prove to be the beginning of a novel antidepressant class and spur the development of other neuropeptide analogs.

Well-characterized abnormalities of the hypothalamic-pituitary-adrenal axis function in depressed subjects has focused attention on the role of corticotrophin-releasing hormone (CRH) in the pathophysiology of major depression and the mechanism of action of antidepressants. Cerebrospinal fluid CRH levels are commonly elevated in depressed populations,[38] as well as in other psychiatric illnesses. Although the significance of this elevation remains unclear, intracerebroventricular application of CRH agonists to animals evokes depression-like symptoms (anorexia, hyperarousal, decreased sexual behaviors, and hypercortisolism). Furthermore, a host of preclinical data suggest that antidepressant administration decreases CRH transmission and sensitivity in laboratory animals and reduces cerebrospinal fluid CRH in depressed patients.[39] Several therapeutic studies indirectly support the role of reduced hypothalamic-pituitary-adrenal axis and CRH function in antidepressant action. For example, steroid suppressant therapy (i.e., aminoglutethimide, metyrapone, and/or ketoconazole) has reduced depressive symptoms in medication-refractory patients.[40] Availability of nonpeptide CRH antagonists for clinical trials will allow further testing of this model.

FOCUSING BEYOND THE RECEPTOR: POSTRECEPTOR SIGNAL TRANSDUCTION

Given that monoamine systems have widespread distribution and potentially target similar neuronal substrates, a common mechanism of antidepressant action may involve effects on postsynaptic, intracellular signal processing. Enhanced monoamine neurotransmission evokes a cascade of intracellular events that ultimately affect gene expression.[30] Most classes of antidepressants have been associated with elevated cAMP levels, which are closely linked to the induction of multiple transcription factors such as cAMP response element binding protein (CREB) in the hippocampus. Increased CREB expression leads to increased expression of multiple genes and proteins, including brain-derived neurotrophic factor

(BDNF). Emerging preclinical data suggest the relevance of BDNF in the pathophysiology of depression and in the mechanism of antidepressant treatments. Animal models of depression have been associated with decreased BDNF levels, and, conversely, intracerebroventricular application of BDNF has antidepressant properties. Protective properties of BDNF against stress or neurotoxin-induced hippocampal atrophy are consonant with observations that recurrent depression is associated with decreased hippocampal volumes.[41] Further focus on intracellular mechanisms may implicate other transcription factors and expressed genes that are relevant to the mechanism of action of antidepressants. In this manner, a genetic-based line of inquiry on the study of antidepressants has the capacity to implicate hitherto unsuspected and/or unknown substrates in models of antidepressant action.

FUNCTIONAL NEUROANATOMY OF ANTIDEPRESSANT ACTION

Over the past decade, a pattern of neuroimaging abnormalities in unmedicated depressed patients has implicated a crude neurocircuitry of depression, and, conversely, antidepressant action.[42,43] Multiple studies utilizing positron emission tomography (PET) or single photon emission computed tomography (SPECT) techniques to assess blood flow or metabolism have demonstrated that unmedicated depressed patients, relative to never-depressed control subjects, have increased activity in the ventral prefrontal cortex and decreased activity in the dorsal prefrontal cortex. Other areas that have been implicated, but less reliably so, include the amygdala, basal ganglia structures, and the anterior cingulate. Treatment response has been linked to normalization of dorsal and ventral activities and may correlate with pretreatment anterior cingulate activity. Methodological and diagnostic factors are thought to contribute to the variance of reported findings.

Although these aforementioned brain regions are highly regulated by input from monoamine and other neurotransmitters, an emerging model suggests that the pathology of depression may lay in specific anatomic substrates as opposed to distributed neurochemical systems. Until recently, there has been almost no capacity to exploit this conception clinically in the treatment of depression. The technique of transcranial magnetic stimulation (TMS) allows for the application of magnetic fields sufficiently strong to alter cortical firing patterns. In controlled trials, TMS applied over the left dorsal frontal cortex has been shown to significantly improve depressive symptoms more than did sham treatment.[44,45] These preliminary results have fueled enthusiastic efforts from multiple groups to assess the efficacy of TMS in depression. Although the anatomic focus of these first studies is consonant with imaging findings, the manner in which the repeated administration of magnetic fields changes the electrophysiologic characteristics of underlying neurons remains unclear.

CONCLUDING COMMENTS

Although immediate pharmacologic targets can be identified for most somatic antidepressant treatments (with notable exceptions of electroconvulsive therapy, TMS, and phototherapy), elucidation of the critical mechanistic steps leading to symptom relief has defied decades of vigorous research. A search for a common mechanism of action that is shared by all antidepressant classes is plausible, albeit potentially unachievable, in that all successful interventions seemingly render patients in qualitatively similar states of remission.

Perhaps the ultimate measure of model of antidepressant action is its clinical power in suggesting improved treatments. Over the past 3 decades, refinements in monoamine-based conceptions have rendered novel treatment regimens (e.g., pindolol and lithium). Nevertheless, persisting clinical limitations in currently available antidepressant strategies call for a rational therapeutics based upon models that extend beyond the monoamines.

Drug names: aminoglutethimide (Cytadren), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), ketoconazole (Nizoral), methyldopa (Aldomet and others), mirtazapine (Remeron), paroxetine (Paxil), pindolol (Visken), reserpine (Serpasil and others), yohimbine (Yocon and others).

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