

New and Emerging Classes of Antidepressants

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Depression is the most common psychiatric disease in the elderly. Over 30% of community-dwelling elderly suffer from subsyndromal depression and over 10% of hospitalized elderly have syndromal major depressive disorder (MDD). Depression is frequently a persistent and recurrent disorder leading to increased morbidity and mortality, as well as poor quality of life.

Early antidepressant medications, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were discovered through astute clinical observations. These first-generation medications are effective because they enhance serotonergic and/or noradrenergic function. Unfortunately, the TCAs also block histaminic, cholinergic and

alpha-1 adrenergic receptor sites, causing unwanted side effects such as weight gain, dry mouth, constipation, urinary retention, confusion, drowsiness and dizziness. MAOIs interact with tyramine to cause potentially lethal hypertension and cause dangerous interactions with a number of prescribed and over-the-counter medications.¹

A major goal of antidepressant development is to improve on preceding drug classes for greater specificity, fewer unwanted side effects and more rapid onset of action. To this end, antidepressants with significantly distinct pharmacological characteristics have been introduced in the last decade (Table 1), including the most widely prescribed single-receptor selective serotonin reuptake

inhibitors (SSRIs). Other multiple-receptor antidepressants, including venlafaxine, mirtazapine, bupropion, trazodone and nefazodone, target one or more specific brain receptor sites with generally fewer side effects than their precursors.^{2,3}

In spite of the remarkable structural diversity, most antidepressants that have been recently introduced modulate monoamine activity as a therapeutic strategy. These newer antidepressants, however, are not ideal, as they require two to six weeks of treatment to produce therapeutic effect and leave approximately 30% of patients unresponsive.^{4,5}

The emergence of potential novel mechanisms of action beyond the monoaminergic synapse may provide an entirely new set of potential therapeutic targets and thus lead to important new developments.⁶ These approaches include the modulation of the neuropeptide substance P, N-methyl-D-aspartate (NMDA), gamma amino butyric acid

Table 1

Mechanisms of Action of Various Antidepressants

Drug	Mechanism of Action
Selective serotonin reuptake inhibitors (SSRIs)	Act predominantly as serotonin (5-HT) reuptake inhibitors
Venlafaxine	Serotonin noradrenaline reuptake inhibitor (SNRI) Blocks 5-HT and noradrenaline (NA) reuptake May also block some dopamine reuptake
Mirtazapine	NA and specific serotonin antagonist (NaSSA) Potent antagonist of central alpha-2 adrenergic autoreceptors and heteroreceptors Antagonist of 5-HT ₂ and 5-HT ₃ receptors Resultant increase in both NA and specific (5-HT ₁) serotonergic transmission
Bupropion	NA and dopamine reuptake inhibitor
Trazodone	5-HT _{2A} antagonist 5-HT reuptake inhibitor with strong alpha-1-antagonism and antihistamine properties
Nefazodone	Weak serotonin reuptake inhibitor (SARI) but powerful 5-HT _{2A} antagonist
Reboxetine	Selective noradrenaline reuptake inhibitor (NARI)

(GABA), the hypothalamic-pituitary-adrenal (HPA) axis and the immune system, and the brain-derived neurotrophic factor (BDNF) to promote neurogenesis.⁷

Substance P Antagonists

During the past decade, considerable progress has been made in understanding the neural circuits involved in the antidepressant and anxiolytic efficacy of the neuropeptide substance P (SP).⁸ Although best known as a pain neurotransmitter, SP also controls vomiting and various behavioural, neurochemical and cardiovascular responses to stress.⁹ Clinical trials have confirmed the efficacy of SP antagonists (SPAs) involving NK1 receptors in alleviating depression and emesis but, surprisingly, not pain. Pharmacological blockade or deletion of the NK1 receptor produces an antidepressant and anxiolytic-like profile in a range of behavioural assays that is distinct from that of established drugs.¹⁰ SPAs are generally well tolerated and do not induce sedation or motor impairment in pre-clinical species. This represents an important opportunity to exploit these molecules as novel therapeutic agents. SPAs are currently the best validated and most clinically advanced novel approach to treating MDD, and several compounds are in advanced clinical development.

N-methyl-D-aspartate

The N-methyl-D-aspartate (NMDA) receptor complex is a subtype of glutamate receptor and its dysfunction is involved in many neurological disorders associated with aging, including chronic pain, depression, stroke and Parkinson's disease. NMDA receptors are crucial for hippocampal cell plasticity and to encode the salient features of experience. Disruption of these plasticity mechanisms may underlie depressive as well as other age-related disorders. Both preclinical and recent clinical studies indicate that compounds which reduce transmission at NMDA receptors are effective antidepressants. Moreover, chronic administration of antidepressants to mice alters

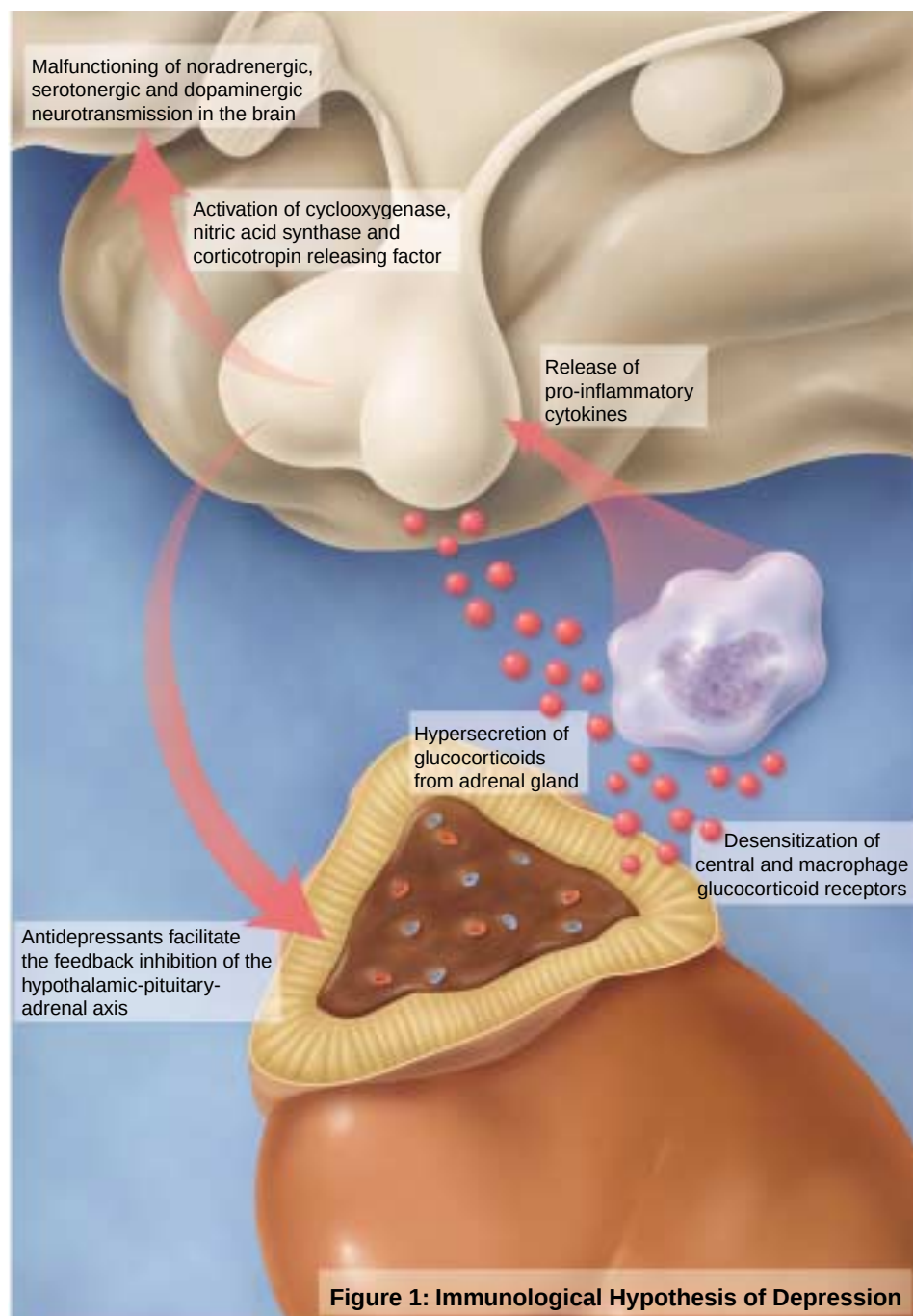


Figure 1: Immunological Hypothesis of Depression

both the mRNA levels encoding NMDA receptor subunits and radioligand binding to these receptors within areas of the brain. It is hypothesized that these two different strategies converge to produce an identical functional endpoint: a region-specific dampening of NMDA receptor function. The pathways leading to this convergence provide a rudimentary framework for discovering novel antidepressants.²

Gamma Amino Butyric Acid

Over the past 20 years, several lines of evidence from preclinical and clinical studies have accumulated to suggest that a GABA deficit may be involved in mood disorders, particularly in depression. Increasing GABA neurotransmission may exert an antidepressant effect and perhaps a mood stabilizing effect.¹¹

Given that GABA has an inhibitory effect on norepinephrine and serotonin, it is thought to complement the biogenic

amine theory of depression. Low GABA function is proposed to be an inherited biological marker of vulnerability for development of mood disorders. Environmental factors, such as stress and excessive alcohol use, may increase GABA, causing symptoms of depression or mania.¹² Either treatment or the passage of time then returns GABA to its presymptomatic baseline as the symptoms remit. Glutamate and GABA systems are emerging as targets for the development of medications for mood disorders. Drugs that reduce glutamatergic activity or glutamate receptor-related signal transduction might also have anti-manic effects. Future research is needed to develop and evaluate new agents with specific glutamate and GABA receptor targets in the treatment of mood disorders.¹³

Hypothalamic-pituitary-adrenal Axis and the Immune System

It is now widely accepted that psychological stress and psychiatric illness can compromise immune function. Both external and internal stressors are well known to activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in hypersecretion of adrenal glucocorticoids (Figure 1). In MDD, the prolonged elevation of glucocorticoid concentration leads to a desensitization of the central glucocorticoid receptors and receptors located on macrophages. These changes may account for the observation that many aspects of cellular immunity are activated in depression. Pro-inflammatory cytokines have been implicated in the pathological changes seen in MDD. Both activation (macrophage activity and acute phase proteins) and inhibition (natural killer cell activity) of the immune system occur in MDD. Many of the behavioural changes seen in depression are simulated by three pro-inflammatory cytokines (IL-1, IL-6 and TNF- α) that affect the brain by activating cyclooxygenase, nitric acid synthase and corticotropin-releasing factor.¹⁴

Effective antidepressant treatment modifies these immune changes. It has been established that some of the pro-inflammatory cytokines are potent acti-

vators of the HPA axis, and there is evidence that the hypersecretion of glucocorticoids and pro-inflammatory cytokines result in the malfunctioning of noradrenergic, serotonergic and dopaminergic neurotransmission in the brain, reflected as symptoms of major depression.¹⁵

Although the precise mechanisms are uncertain, there is evidence that antidepressants reduce the release of pro-inflammatory cytokines from activated macrophages and thereby facilitate the feedback inhibition of the HPA axis. This results in a reduction in the release of glucocorticoids from the adrenal glands. In addition, many antidepressants have been shown to increase the release of endogenous cytokine antagonists such as interleukin-1 receptor antagonist and interleukin-10. There is evidence demonstrating that different classes of antidepressants act as cyclooxygenase inhibitors which, by lowering the concentration of inflammatory prostaglandins in the brain, reduce the detrimental impact of the inflammatory changes on neurotransmitter function.¹⁶

An advantage of the macrophage hypothesis is that it goes further than the biogenic amine hypothesis of depression by taking into account changes in the endocrine and immune systems, which also play crucial roles in the etiology of depression and broaden the basis of understanding of antidepressant mechanism of action.¹⁷

More research is needed to investigate the interrelationships between the various pro-inflammatory cytokines and the behavioural changes invoked in MDD. The immunological hypothesis has been important for stimulating new concepts in the causes of the pathological changes in MDD, and how effective drug treatments may attenuate them.

Brain-derived Neurotrophic Factor & Neurogenesis

Although the majority of neurons in the forebrain of mammals are formed prenatally, scientists have learned over the past few years that certain areas of the adult brain can produce new neurons, includ-

ing the hippocampus and the subventricular zone (a cell layer surrounding the lateral ventricles of the forebrain).¹⁸ Demonstration of neurogenesis in the adult brain represents a major advance in our understanding of the cellular mechanisms underlying neuronal remodeling and complex behaviour.^{19,20}

Exogenous delivery of the neurotrophic factors, brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3) promotes the function, sprouting and regrowth of serotonin-containing neurons in the brains of adult rats. Similar infusions of BDNF into the dorsal raphe nucleus produce an antidepressant effect, as evaluated by several "learned helplessness" paradigms. Environmental stressors, such as immobilization, induce depression and decrease BDNF mRNA levels, whereas antidepressants prevent these stress-induced reductions of BDNF mRNA levels in the brain.^{21,22} Existing treatments of depression might work by increasing endogenous brain levels of BDNF or NT-3, which in turn could promote monoamine-containing neuron growth and function. Neurogenesis is up-regulated by antidepressants that are serotonin (5-HT) or noradrenaline reuptake inhibitors in adult rodent hippocampus. Up-regulation of neurogenesis could block or reverse the effects of stress on hippocampal neurons, which include down-regulation of neurogenesis as well as atrophy. Transduction of the cAMP signal cascade may form the basis of regulation of neurogenesis by antidepressants. Clinical studies must be conducted to determine the significance of adult neurogenesis in humans. These findings will stimulate new avenues of research to identify the cellular and molecular stress-related mood disorders, as well as the development of novel therapeutic strategies. Medications that selectively stimulate the production of neurotrophins could represent a new generation of antidepressants.

Antidepressant medications and electroconvulsive therapy typically require three to six weeks before their benefits are observed. It is suggested that

this period reflects the time it takes for newly-born dentate gyrus neurons to fully mature, extend their neurites and integrate with the existing brain circuitry. Serotonin can dramatically augment cell proliferation, at least in part, by action at the 5-HT_{1A} receptor.²³ Consistent with this observation, the hippocampus—especially the dentate gyrus—has an extremely dense concentration of 5-HT_{1A} receptors. Decreased expression of 5-HT_{1A} mRNA has been found in the hippocampus of depressed suicide victims. These findings provide additional support for this receptor's importance in controlling depression. If this receptor plays a role in depression, it would be useful to test 5-HT_{1A}-agonist drugs as therapeutic agents. Although a potent and specific 5-HT_{1A}-receptor agonist for human use is currently unavailable, partial 5-HT_{1A} agonists do exist and reduce anxiety while providing some AD effect.

Conclusion

In summary, early antidepressants (e.g., MAOIs and TCAs) are effective but not well tolerated. Several chemically unrelated agents (e.g., SSRIs, SNRIs, mirtazapine, nefazodone and moclobamide) have been introduced in the past decade. In spite of the remarkable structural diversity, most currently prescribed antidepressants are monoamine based and are far from ideal due to undesirable side effects, slow onset of action and ineffectiveness in a significant number of patients. New antidepressants with potentially novel mechanisms are on the horizon. ♦

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