Table 2. Additional Biologic Theories of the Pathophysiology of Depression.*

Theory	Supporting Evidence	Contradictory Evidence
Altered glutamatergic neurotransmission	Glutamate and glutamine levels in the prefrontal cortex are reduced[91]	Glutamate levels in the occipital cortex are increased[92,93]
	Intravenous ketamine, an NMDA antagonist, induces rapid, sustained antidepressant effect [94]	Ketamine binds to high-affinity-state D2 dopamine receptors[95]
	Cortical messenger RNA levels of glutamate transporters and of the enzyme that converts glutamate to glutamine are reduced[96]	It is not clear whether antidepressants affect AMPA receptors in the brain[97]
Reduced GABAergic neurotransmission	Levels of GABA in plasma, cerebrospinal fluid, the dorsolateral prefrontal cortex, and the occipital cortex are reduced[91-93]	GABA occurs in more than 30% of brain synapses, suggesting nonspecificity
	GABA-modulating agents have effects in animal models of depression[98]	There is a lack of difference in prefrontal cortex GABA levels on MRS in depression[99]
	Antidepressants affect GABAergic function[98]	GABA neurotransmission may be related to symptoms of anxiety in depression
	GABA neuron immunoreactivity is reduced in the prefrontal cortex[100]	
Abnormal circadian rhythms	Sleep deprivation and light therapy have antidepressant effects[101,102]	The association between clock-related genes and depression is inconsistent[103]
	Some patients with depression have circadian abnormalities of mood, sleep, temperature, and neuroendocrine secretion[104]	
	Rodents active during the day become depressed when daylight is shortened[105]	
Deficient neurosteroid synthesis	Cholesterol levels are low in plasma and the brain during depression[106]	The findings in schizophrenia are similar[107]
	DHEA has antidepressant effects in patients with depression[108]	Neurosteroids (neuroactive steroids in the brain that modulate neurotransmitter receptors) mostly affect memory and sleep
Impaired endogenous opioid function	δ-Opioid–receptor agonists have antidepressant-like effects in rodents and up-regulate levels of BDNF in the brain[109]	Although early reports suggested that opiates may be effective in treating depression,[110] data from large, controlled, randomized trials are lacking
	Capacity for cortical μ-opioid–receptor binding is decreased in response to sustained sadness[111]	
Monoamine–acetylcholine imbalance	Depressed mood can be induced in humans by administration of physostigmine, an acetylcholinesterase inhibitor[112]	Mecamylamine, a nicotinic acetylcholine receptor antagonist, reduced symptoms of depression[113]
	Nicotinic acetylcholine receptor antagonists potentiate antidepressants[114]	Many antidepressants are not anticholinergic
Cytokine-mediated cross-talk between the immune system and the brain	Depression is common in infectious and autoimmune diseases[115]	Most studies are correlative[116]
	Exposure to cytokines induces depressive symptoms, and cytokine secretion is increased in major depression[115]	Cytokine-induced depressive symptoms are temporary and not replicated in all studies[117]
	Antidepressants have antiinflammatory effects[115]	Substance P antagonists are not therapeutic in depression
	Cytokines affect the hypothalamic–pituitary–adrenal axis and monoamines[115]	

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Thyroxine abnormalities	Levels of transthyretin are reduced in the cerebrospinal fluid in patients with depression[118]	
	Thyroid hormones modulate the serotonergic system in the brain[119]	Thyroxine monotherapy is ineffective
	Brain neurogenesis is decreased after the administration of thyroxine in adult rats with hypothyroidism[120]	Hypothyroidism is not manifested in most patients with depression
	Rate of response to triiodothyronine is increased during depression[121]	
Dysfunction of specific brain structures and circuits	Transcranial magnetic stimulation of the prefrontal cortex[122] and deep-brain stimulation of the anterior cingulate affect mood[123]	Implicated brain areas differ from study to study
	Glucose use is reduced in the prefrontal cortex[124] and subgenual prefrontal cortex[125]	Inconsistent findings with respect to blood flow, volumetric, glucose utilization, and postmortem methodologies[63,124,126]
	Circuit dynamics in the hippocampus are altered in a rat model of depression[127]	

* AMPA denotes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BDNF brain-derived neurotrophic factor, DHEA dehydroepiandrosterone, GABA γ-aminobutyric acid, MRS magnetic resonance spectroscopy, and NMDA *N*-methyl-D-aspartic acid.

stress associated with mental arithmetic calculations or simulated public speaking, results in greater changes in plasma cortisol levels than most reported differences between the values in patients with depression and those in controls.[38] It is possible that chronic mild elevations of cortisol, especially at night, when cortisol levels in normal subjects are very low, have a pathogenic role in depression. It is also possible that peripheral cortisol elevations are only a reflection of central disturbances in CRH signaling, which mediate the effects of environmental stress on mood.[59] A major liability of the hypothalamic–pituitary–adrenal axis theory of depression is the difficulty of defining the relationship of stress to depression. Some patients have a single lifetime depressive episode, whereas a larger proportion have a recurrent or even chronic course. Various types of acute stress, early childhood trauma, or long-term psychosocial problems may be involved and may lead to different responses of the stress system. Stress may be causative in some cases and secondary to depressed mood in others.

Severe stress in rodents does not necessarily model the common stresses of childhood. The association of abuse in childhood with psychopathologic disorders, including depression, in adulthood could be due to common factors linking family perpetrators of abuse and their victims, including not only shared genes but also a shared environment of poverty, poor nutrition, and poor prenatal care. Depression is not uncommon in people with no psychosocial risk factors. Most patients treated for depression have no evidence of hypothalamic–pituitary–adrenal dysfunction, just as most such patients have no direct evidence of brain monoamine deficiency.

The classic teaching is that neurons do not divide in the adult mammalian brain, but studies have shown that neurogenesis occurs in several areas of the brain, especially the hippocampus. Neurogenesis is more prominent in rodents than in primates,[60] and some have questioned whether it occurs in the human cortex.[61] Elevated levels of glucocorticoids can reduce neurogenesis, and this has been suggested as a mechanism for the decreased size of the hippocampus on magnetic resonance images of the brain in many patients with depression.[62] In postmortem studies of patients with depression, cell loss in the subgenual prefrontal cortex, atrophy in the dorsolateral prefrontal cortex and the orbitofrontal cortex, and

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