Fig. 103-1A. (A) Schematic representation of a catecholamine neuron and biosynthetic pathway to production of dopamine (DA) and norepinephrine (NE). The catecholamine neuron is impinging on a postsynaptic target that has DA (D₁, D₂, D₃, D₄, D₅) and NE (α₁, α₂, β₁, β₂, β₃) receptors linked to second-messenger signaling and intracellular events. The amino acid L-tyrosine is actively transported into presynaptic catecholamine nerve terminals and converted to catecholamines. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (levodopa), a drug used in treatment of Parkinson disease, by the enzyme tyrosine hydroxylase (TH). Notably, α-methyl-p-tyrosine (AMPT) is a competitive inhibitor of TH and results in reduced catecholaminergic function in clinical studies of mood disorders. Aromatic amino acid decarboxylase (AADC) takes levodopa to DA down the synthetic pathway. DA is then taken up from the cytoplasm and packaged into vesicles by vesicle monoamine transporters (VMATs) to await release into the synapse. However, DA can also be hydroxylated by dopamine-β-hydroxylase (DBH) in the presence of O₂ and ascorbate to form NE. Norepinephrine (NM) is formed by the action of catechol-O-methyltransferase (COMT) on NE and is then further metabolized by monoamine oxidase (MAO) and aldehyde dehydrogenase to 3-methoxy-4-hydroxyphenylglycol (MHPG). Tropisetron is an agent that can block COMT. Phenylalanine, selegiline, and tranylcypromine are antidepressants that inhibit MAO. Reserpine causes a depletion of monoamines from vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported). Once released from the presynaptic terminal, DA can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of NE and DA neuron firing activity and release occurs through somatodendritic (not shown) and nerve-terminal α₂-adrenoceptors and D₂ receptors, respectively. Yohimbine potentiates NE neuronal firing and NE release by blocking these presynaptic α₂-adrenoceptors, thereby distibuting these neurons from a negative feedback influence. This agent can also induce panic attacks in individuals that are prone to this disorder. Conversely, clonidine attenuates NE neuron firing and release by activating presynaptic α₂-adrenoceptors. This antihypertensive agent can help with reducing opiate withdrawal symptoms and is often used in children with attention-deficit hyperactivity disorder (ADHD). Idazoxan is a relatively selective α₂-adrenoceptor antagonist primarily used for pharmacological purposes and guanfacine is used in treatment of ADHD. Aripiprazole is a non-selective partial D₂ receptor agonist and antipsychotic agent used in treatment of mood disorders. The binding of NE to G protein receptors (Go, Gi, etc.) coupled to adenylyl cyclase (AC) and phospholipase C-β (PLC-β) produces a cascade of second messenger and cellular effects (see diagram and later sections of the text). Propranolol (β₂-receptor antagonist) has beneficial effects in situational anxiety and prazosin (α₁-receptor antagonist) reduces nightmares associated with posttraumatic stress disorder (PTSD; both agents are antihypertensives). NE has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron via NE transporters (NETs). Once inside the neuron it can either be repackaged into vesicles for reuse or undergo enzymatic degradation. The selective NE reuptake inhibitor antidepressant reboxetine and older-generation tricyclic antidepressant desipramine are able to interfere/block the reuptake of NE. On the other hand, amphetamine is able to facilitate NE release by altering NET function. Cocaine and bupropion exert effects in part, through nonselective blockade of DA transporters (DAT). Note: green spheres represent DA neurotransmitters; blue spheres represent NE neurotransmitters. (B) Schematic representation of a serotonin (5-HT) neuron and its postsynaptic target. 5-HT is produced from L-tryptophan, an amino acid actively transported into presynaptic 5-HT-containing terminals. It is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme tryptophan hydroxylase (TrpH). This enzyme is effectively inhibited by the drug p-chlorophenylalanine (PCPA), a depressogenic agent. Aromatic amino acid decarboxylase (AADC) converts 5-HTP (a 5-HT enhancer) to 5-HT. Once released from the presynaptic terminal, 5-HT can interact with a variety (i.e., 15 different types) of presynaptic and postsynaptic receptors. Presynaptic regulation of 5-HT neuron firing activity and release occurs through somatodendritic 5-HT₁A (not shown) and 5-HT₁D autoreceptors, respectively, located on nerve terminals. Buspirone is a partial 5-HT₁A receptor agonist that activates both pre- and postsynaptic receptors and is a non-benzodiazepine receptor agonist used in treatment of anxiety. Vilazodone is a newer selective serotonin reuptake inhibitor (SSRI) and partial 5-HT₁A, 5-HT₁B receptor agonist. The binding of 5-HT to G-protein receptors (Go, Gi, etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C-β (PLC-β) will result in the production of a cascade of second-messenger and cellular effects. Lysogenic acid diethylamide (LSD) likely interacts with numerous 5-HT receptors to mediate its effects. 5-HT has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron through 5-HT transporters (5-HTT). Once inside the neuron it can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. The SSRIs and older-generation tricyclic antidepressants (TCAs) are able to interfere/block the reuptake of 5-HT (agents such as fluoxetine, paroxetine, sertraline, and citalopram are examples). Venlafaxine and duloxetine are SNRIs, i.e., serotonin and norepinephrine reuptake inhibitors, which enhance the availability of both these monoamines. 5-HT is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO), located on the outer membrane of mitochondria or sequestered and stored in secretory vesicles by vesicle monoamine transporters (VMATs). Reserpine causes a depletion of 5-HT in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this agent). Tranylcypromine and phenylzine are MAOIs and effective antidepressants. Fenfluramine (an anorectic agent) and MDMA (“ecstasy”) are able to facilitate 5-HT release by altering 5-HTT function. DAG, diacylglycerol; 5-HTT, serotonin transporter; IP₃, inositol-1,4,5-triphosphate.
on a postsynaptic target that has DA (D1, D2, D3, D4, D5) and NE (α1, α2, β1, β2, β3) receptors linked to second-messenger signaling and intracellular events. The amino acid L-tyrosine is actively transported into presynaptic catecholamine nerve terminals and converted to catecholamines. The rate-limiting step is conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA, a drug used in treatment of Parkinson disease) by the enzyme tyrosine hydroxylase (TH). Notably, o-methyltyramine (OMT) is a competitive inhibitor of TH and results in reduced catecholaminergic function in clinical studies of mood disorders. Aromatic amino acid decarboxylase (AADC) takes L-DOPA to DA down the synthetic pathway. DA is then taken up from the cytoplasm and packaged into vesicles by vesicle monoamine transporters (VMATs) to await release into the synapse. However, DA can also be hydroxylated by dopamine-β-hydroxylase (DBH) in the presence of O2 and ascorbate to form NE. Normetanephrine (NM) is formed by the action of catechol-O-methyltransferase (COMT) on NE and is further metabolized by monoamine oxidase (MAO) and aminohydrolase to 3-methoxy-4-hydroxyphenylglycol (MHPG). Tropolone is an agent that can block COMT.

The glutamate system has now presented itself as a viable target in antidepressant action. This figure schematically represents various processes involved in glutamatergic regulation and neurotransmission. Synthesis of glutamate derives from glucose and undergoes transamination to α-ketoglutarate; however, a small proportion of glutamate can be formed from glutamine by glutamine synthetase. Conversion of glutamine to glutamate occurs in glia cells and can then be transported to neurons, with mitochondria glutaminase being needed to complete the formation of glutamate from its precursors. Glutamate can also undergo oxidation to yield α-ketoglutarate in astrocytes and transported to neurons for glutamate synthesis and vesicular storage. Calcium-dependent excitotoxic processes control glutamate release and this neurotransmitter can impact a variety of postsynaptic receptors (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and metabotropic [mGluR]). The mGluR2 and mGluR3 localization on glutamate neurons confer autoreceptor capabilities and targeting these receptors or reuptake transporters (found on neurons [GTn] and astrocytes [GTg]) have been proposed to be viable antidepressant targets. Reductions in astrocytes are documented in mood disorders and possibly contribute to glutamatergic deregulation, with glial-derived neurotrophic factor (GDNF) and S100β secreted from these cells being important in maintaining synapse integrity. 5-HT1A receptors are important in antidepressant action and can modulate the release of S100β, potentially bridging 5-HT regulation of the glutamate system and synapse plasticity. Listed in this figure are agents that biochemically target glutamate receptors and have the potential to mediate antidepressant effects. However, none of them are as yet FDA approved for clinical use. Glu, glutamate; Gly, glycine; GTg, glutamate transporter glial; GTn, glutamate transporter neuronal; mGluR, metabotropic glutamate receptor; purple sphere, glutamate; green arrow, agonist; red line, antagonist.
Fig. 103-3. Schematic representation of a midsagittal section of the human brain (center). Circular blowout representation of neurotransmitter–receptor transduction mechanisms to biogenic amines and glutamate signaling implicated in antidepressant action (bottom left). Specifically, activation of G protein-coupled receptors can mediate changes in second messengers, such as adenylate cyclase and calcium (Ca^{2+}) transduction. This impacts various intracellular components deemed important in antidepressant action, such as changes in cAMP and calcium. Activation of α1-adrenoceptors directly on 5-HT neurons mediates NE effects in the dorsal raphe (not shown). As most antidepressants biochemically target 5-HT and/or NE neuron elements, their reciprocal interactions and neural changes to enhance monoamine neurotransmission may lead to different regulatory set-points of forebrain activation. Circular blowout representation of the hypothalamic-pituitary adrenal (HPA) axis with notable neurohormones implicated in mood and anxiety (bottom right). These neurohormones can shape neural circuits and the stress–anxiety–depression axis. Circular blowout representation of glutamate receptors (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]), nicotinic receptor (nAChR), adenosine receptor (A1), voltage-gated Ca^{2+} channel (VGCC), and calcium transporter (Ca^{2+}T), with intracellular mitochondria, endoplasmic reticulum, and membrane bound receptors able to change Ca^{2+} dynamics and neuronal function. These processes have been implicated in depression as either viable treatment targets or mutations that may contribute to mood disorders (top right). Circular blowout representing an example of a unified mechanism by which mood regulating agents can change intracellular components, such as PKC and calmodulin (CaM) mediated signaling. Phosphorylation states of proteins and enzymes, which can alter cellular activity profiles, may be important intermediates in antidepressant action. For instance, effector proteins that are bound to CaM (i.e., presynaptic localized GAP by, postsynaptic localized neurogranin) can regulate Ca^{2+} signaling set-points through their phosphorylation state and lead to altered activation of CaMKII (calcium-dependent protein kinase II), circuit activity, and potentially mood regulation. Presynaptic GAP and postsynaptic neurogranin are major phosphorylation targets of PKC and together can shape neurotransmitter release profiles and postsynaptic events to numerous psychotropic agents.50,127