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THERAPEUTIC TARGETS FOR BIPOLAR DISORDER

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ABSTRACT

Bipolar disorder is a psychiatric illness characterized by dramatic mood swings in which an individual experiences periods of highs (euphoria) and lows (sadness), referred to as episodes of mania and depression, respectively. Standard treatment options for the disorder have varied considerably over the years. In general, pharmacotherapy with lithium or the antiepileptic agent lamotrigine is considered first-line monotherapy for acute bipolar depression in patients not already on a mood stabilizer. However, it is unlikely that there is a single treatment that would be effective in all phases of the disorder and in all patients. Researchers actively continue to search for effective treatments for bipolar disorder with special attention given to the identification of novel targets for therapeutic intervention. This article presents those drug targets that are currently under active investigation for the treatment of bipolar disorder.

INTRODUCTION

Bipolar disorder, also known as manic–depressive illness, is defined by the National Institutes of Mental Health (NIMH) as "a brain disorder that causes unusual shifts in a person's mood, energy, and ability to function." The disorder involves dramatic mood swings from overly euphoric and/or irritable to sad/hopeless, and then back again, often with periods of normal mood in between; severe changes in energy and behavior accompany these changes in mood. The periods of highs and lows are called episodes of mania and depression. The classic form of the disorder is known as bipolar I disorder and is comprised of recurrent episodes of mania and depression. Some individuals never develop severe mania, but instead experience milder episodes of hypomania that alternate with depression; this form of the illness is called bipolar II disorder. When 4 or more episodes of illness occur within a 12-month period, a patient is said to have rapid-cycling bipolar disorder. Some people experience multiple episodes within a single week, or even within a single day. Rapid cycling tends to develop later in the course of illness, and is more common among women than men; it has also been identified as a predictor of nonresponse to treatment. In other patients, symptoms of mania and depression may coexist in what is referred to as a mixed bipolar state, where an individual may experience a very sad, hopeless mood and feel extremely energized at the same time (1-3).

According to the NIMH, bipolar disorder affects approximately 2.3 million adult Americans. The lifetime prevalence of bipolar spectrum disorders overall has been reported to be in the range of 2.8-6.5% in the community, although among patients with major depression the prevalence of bipolar spectrum disorders may be as high as 50% (3, 4). Similar epidemiology has been reported in Europe (5). However, bipolar disorder is believed to be widely under-recognized in the primary care setting, suggesting that its actual prevalence could be much higher (6, 7).

The cause of bipolar disorder is not known. However, it is now generally accepted that some combination of as-yet-undetermined genetic and environmental factors leads to a vulnerability to developing bipolar disorder. The amygdala has been identified as a potentially important element in the etiology of bipolar disorder. Abnormalities in the structure and function of the amygdala itself, as well as deficits in the area of the prefrontal cortex which modulates amygdala activity, have been identified in neuroimaging studies (1, 8).

Different treatment strategies for bipolar disorder are required as the patient progresses from an acute episode, through the process of functional recovery and over the course of maintenance therapy. Thus, it is unlikely that there is a single treatment that would be effective in all phases of the disorder and in all patients (9). Standard treatments for bipolar mania have varied significantly over the years and have at one time or another included bromides, barbiturates, morphine, electroconvulsive therapy and neuroleptic agents. The typical antipsychotic agent chlorpromazine was the treatment of choice during the 1950s, but was replaced by haloperidol, another typical antipsychotic, in the late 1960s. In the 1970s, lithium became the treatment of choice. The majority of research to date has focused on the acute treatment of mania in the bipolar patient, with the result that depression, which is often the predominant symptom of the disorder, is undertreated. Antidepressant therapy is an essential component of effective treatment for bipolar disorder, and may involve the administration of lithium, lamotrigine, atypical antipsy-

chotics and/or antidepressants, including selective serotonin reuptake inhibitors (SSRIs) (1, 10-12).

The American Psychiatric Association (APA) considers lithium or the antiepileptic agent lamotrigine as first-line monotherapy for acute bipolar depression in patients not already on a mood stabilizer. In addition, the APA advises the use of lamotrigine as one of three therapy options for acute depressive episodes in initial nonresponders, as a monotherapy treatment alternative for rapid cycling, and as a treatment alternative along with carbamazepine or oxcarbazepine in bipolar patients requiring maintenance therapy. Treatment alternatives are advocated when first-line therapy is not fully effective, not tolerated or inappropriate for the patient. Adjunctive therapy in initial responders is recommended when patients do not fully respond to treatment after the dose is optimized. Antidepressant monotherapy is not indicated in the treatment of bipolar depression, as it may trigger episodes of mania or induce a pattern of rapid cycling (1, 10-12).

The search for effective treatment strategies for bipolar disorder continues, with special attention given to the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Figure 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

TARGETS

Dopamine D_1 receptor

The D_1 receptor is a seven-transmembrane-spanning G protein-coupled receptor (GPCR; $G_{s/olf}$) that binds to the neurotransmitter dopamine present in the central nervous system (CNS) in basal ganglia. Dopamine is the precursor of norepinephrine and epinephrine and accounts for 90% of all catecholamines. The D_1 receptor subtype stimulates the synthesis of cAMP mainly via coupling to $G_{\alpha s}$ proteins in neurons. Excessive dopamine stimulation of D_1 receptors impairs prefrontal function via cAMP intracellular signaling, which leads to a disconnection of prefrontal networks. Genetic studies indicate that the genes disrupted in serious mental illnesses such as bipolar disorder and schizophrenia often encode for the intracellular proteins that serve as brakes on the intracellular stress pathways. Specifically, the disrupted in schizophrenia 1 protein (*DISC1*) normally regulates cAMP levels, while regulator of G protein-signaling 4

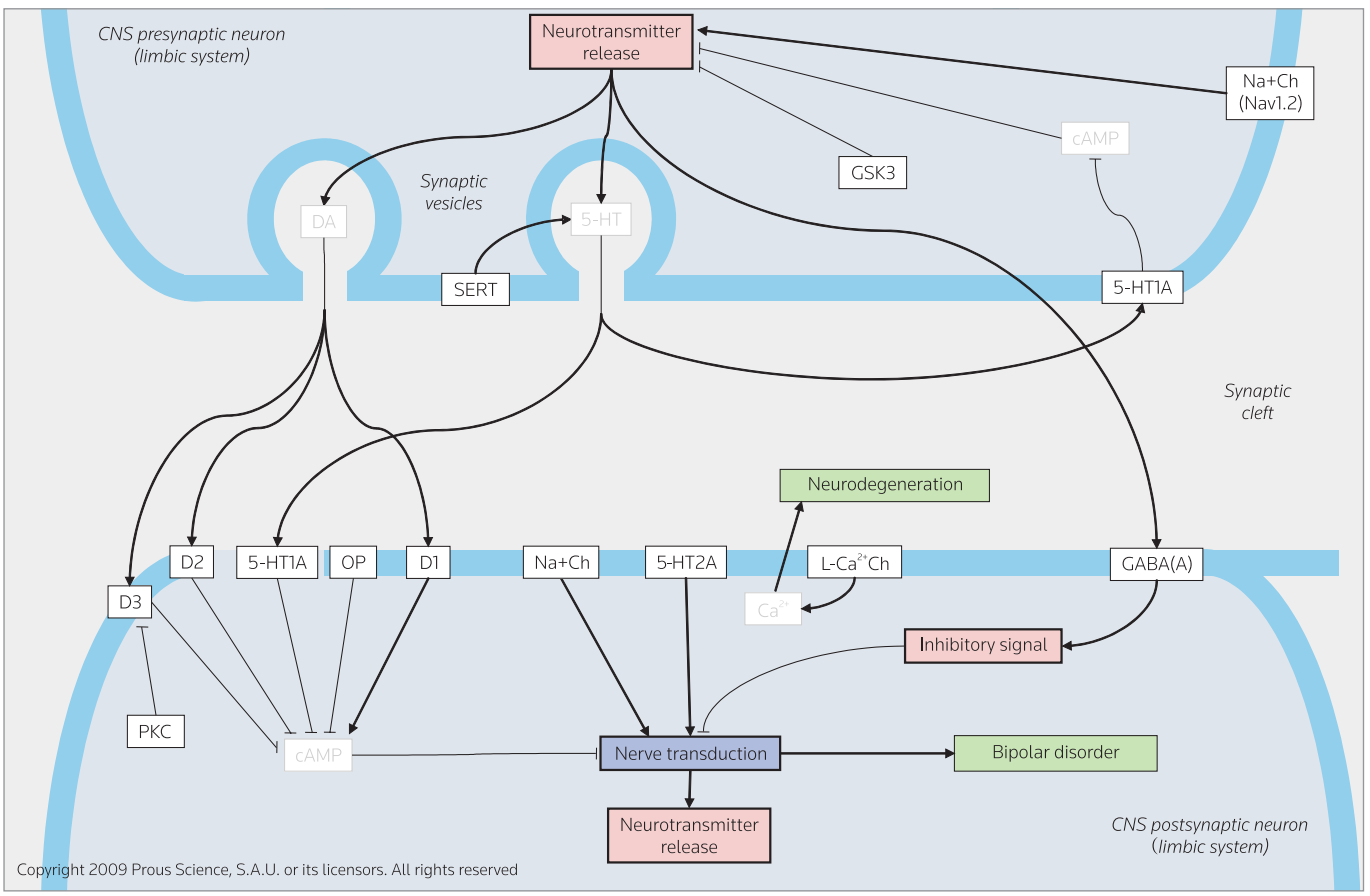

Figure 1. Bipolar disorder targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of bipolar disorder. Arrow: positive effect; dash: negative effect. Abbreviations: CNS: central nervous system; 5-HT1A: serotonin receptor subtype 1A; 5-HT2A: serotonin receptor subtype 2A; Ca^{2+}: calcium ions; cAMP: cyclic adenosine monophosphate (cyclic AMP or 3′-5′-cyclic adenosine monophosphate); D1: dopamine receptor subtype 1; D2: dopamine receptor subtype 2; D3: dopamine receptor subtype 3; DA, dopamine; GABA(A): GABA receptor subtype A; GSK3: glycogen synthase kinase-3; L-Ca^{2+}Ch: L-type calcium channel; OP: opioid receptor; PKC: protein kinase C; SERT: serotonin transporter; Na+Ch: sodium channel; Na+Ch (Nav1.2): voltage-gated sodium channel alpha subunit $Na_v1.2$.

Table I. *Select targets and products launched or being actively investigated for bipolar disorder (from Prous Science Integrity®).*

Target	Product	Source	Phase
Dopamine D_1 receptor	Asenapine maleate	Schering-Plough	Prereg.
Dopamine D_2 receptor	Risperidone	Janssen	L-2003
	Aripiprazole	Bristol-Myers Squibb/Otsuka	L-2004
	Olanzapine	Lilly	L-2004
	Quetiapine fumarate	AstraZeneca	L-2006
	Asenapine maleate	Schering-Plough	Prereg.
	Paliperidone	Johnson & Johnson	Prereg.
	Bifeprunox mesilate	Lundbeck/Solvay	III
	Ziprasidone HCl	Pfizer	III
	Cariprazine HCl	Forest/Gedeon Richter	II
	Iloperidone	Vanda Pharmaceuticals	I
Dopamine D_3 receptor	Cariprazine HCl	Forest/Gedeon Richter	II
$GABA_A$ receptor	Felbamate	National Institute of Mental Health	II
Glycogen synthase kinase-3 (GSK-3)	Lithium carbonate	Noven Therapeutics	L-1939
5-HT_{1A} receptor	Aripiprazole	Bristol-Myers Squibb/Otsuka	L-2004
	Bifeprunox mesilate	Lundbeck/Solvay	III
5-HT_{2A} receptor	Risperidone	Janssen	L-2003
	Aripiprazole	Bristol-Myers Squibb/Otsuka	L-2004
	Olanzapine	Lilly	L-2004
	Quetiapine fumarate	AstraZeneca	L-2006
	Ziprasidone HCl	Pfizer	III
	Iloperidone	Vanda Pharmaceuticals	I
L-type calcium channel	MEM-1003	Memory Pharmaceuticals/Stanley Medical Research Institute	II
Opioid receptors	Pentazocine HCl	Mclean Hospital	II
Protein kinase C (PKC)	Chelerythrine Cl	Marinus Pharmaceuticals	Preclinical
	Tamoxifen citrate	National Institute of Mental Health	II
Serotonin transporter (SERT)	Olanzapine/fluoxetine HCl	Lilly	L-2004
Sodium channel	Lamotrigine	GlaxoSmithKline	L-2003
	Carbamazepine	Validus Pharmaceuticals	L-2005
	Riluzole	National Institute of Mental Health	II
	GSK-1014802	GlaxoSmithKline	I
	JZP-4	Jazz Pharmaceuticals	I
	NW-3509	Newron	Preclinical
Voltage-gated sodium channel $Na_v1.2$	JZP-4	Jazz Pharmaceuticals	I

(*RGS4*) and diacylglycerol kinase eta (*DGKH*), a molecule associated with bipolar disorder, normally serve to inhibit phosphatidylinositol–protein kinase C (PKC) intracellular signaling. Individuals with mutations resulting in loss of adequate function of these genes are likely to have weaker endogenous regulation of these stress pathways and become vulnerable to profound stress-induced prefrontal cortical dysfunction, which induces debilitating symptoms such as thought disorder, disinhibition and impaired working memory. D_1 receptor antagonists may therefore be effective in the treatment of mental illnesses, including schizophrenia and bipolar disorder (13, 14).

Dopamine D_2 receptor

The D_2 receptor is a GPCR (G_i/G_o) that, like the D_1 receptor, binds dopamine present in the CNS in basal ganglia. The D_2 receptor inhibits cAMP synthesis by coupling to $G_{\alpha i/o}$ and also regulates Ca^{2+} and potassium ion channels via phospholipase C (PLC), when it forms hetero-oligomers, particularly with the D_1 receptor. This D_1–D_2 receptor hetero-oligomer has been proposed to facilitate a distinctive dopamine-mediated Ca^{2+} signal, with important effects on synaptic plasticity. In illnesses such as bipolar disorder, schizophrenia, Parkinson's disease and restless legs syndrome, transmission in discrete dopamine pathways may involve a range of hypoactivation to hyperactivation of dopamine receptors, particularly those of the D_2 subtype. Thus, antagonism of this receptor subtype may be an effective treatment approach. However, full agonists or pure D_2 receptor antagonists may not be optimal therapeutic approaches due to their inability to restore the aberrant dopamine pathways to a normal level of basal tone. Dopamine D_2 receptor partial agonists, on the other hand, may stabilize activity in dopamine pathways by dampening excessive and/or restoring deficient D_2 receptor stimulation and achieving a desired level of basal activity. The D_2 receptor is currently one of the most widely studied targets for antipsychotic drugs and D_2 antagonists and D_2 partial agonists have been validated for the treatment of psychiatric diseases such as schizophrenia, anxiety, depression and bipolar disorder (14, 15).

Table II. *Selected patents for targets being pursued or explored for bipolar disorder (from Prous Science Integrity®).*

Target	Patent	Source	Phase
Dopamine D_2 receptor	WO 2003082877	Lilly	Biological testing
	WO 2005019215	Pfizer	Biological testing/preclinical
	WO 2005121113	Janssen	Biological testing/preclinical
	WO 2006056600	Janssen	Biological testing
	WO 2006073886	Lilly	Biological testing
	WO 2006079637	Janssen	Biological testing
	WO 2006134163	Janssen	Biological testing
	WO 2007007132	Egis Pharmaceuticals	Biological testing
	WO 2008020306	Pfizer	Biological testing
	WO 2008124030	Merck & Co.	Biological testing
	WO 2006056600	Janssen	Biological testing
Dopamine D_3 receptor	WO 2006091703	Novasite Pharmaceuticals	Biological testing
	JP 2008214274	Tama Biochemical	Preclinical
Glycogen synthase kinase-3 (GSK-3)	WO 2006091737	Kemia	Biological testing
	WO 2008057940	Vertex Pharmaceuticals	Biological testing
	WO 2008077086	Vertex Pharmaceuticals	Biological testing
	WO 2008077138	University of Illinois	Biological testing/preclinical
	WO 2008112651	Vertex Pharmaceuticals	Biological testing
	WO 2008112642	Vertex Pharmaceuticals	Biological testing
	WO 2008112646	Vertex Pharmaceuticals	Biological testing
	WO 1998042339	University of Chicago's Office of Technology & Intellectual Property/ Dana-Farber Cancer Institute	Preclinical
5-HT_{1A} receptor	US 2008167319	Pfizer	Biological testing
	WO 2006056600	Janssen	Biological testing
	WO 2007007132	Egis Pharmaceuticals	Biological testing
	WO 2008020306	Pfizer	Biological testing
5-HT_{2A} receptor	WO 2003082877	Lilly	Biological testing
	WO 2005121113	Janssen	Biological testing/preclinical
	WO 2006073886	Lilly	Biological testing
	WO 2006079637	Janssen	Biological testing
	WO 2006134163	Janssen	Biological testing
	WO 2007007132	Egis Pharmaceuticals	Biological testing
	WO 2008020306	Pfizer	Biological testing
	WO 2008124030	Merck & Co.	Biological testing
5-HT_{2C} receptor	WO 2006079637	Janssen	Biological testing
	WO 2006116165	Wyeth	Biological testing
	WO 2008052075	Wyeth	Biological testing
	WO 2008052078	Wyeth	Biological testing
	WO 2008052086	Wyeth	Biological testing
	US 2008167319	Pfizer	Biological testing
Protein kinase C (PKC)	WO 2002013803	University of Chicago's Office of Technology & Intellectual Property/ Dana-Farber Cancer Institute	Preclinical
	WO 2005030143	Yale University	Preclinical
	WO 2008016596	Marinus Pharmaceuticals	Biological testing
	WO 2008118403	Yale University	Preclinical
	WO 2005019215	Pfizer	Biological testing/preclinical
Serotonin transporter (SERT)	WO 2006056600	Janssen	Biological testing
	WO 2007042239	GlaxoSmithKline	Biological testing
Sodium channel	WO 2007042250	GlaxoSmithKline	Biological testing
	WO 2008090116	GlaxoSmithKline	Biological testing/phase II
	WO 2008122546	GlaxoSmithKline	Biological testing
	WO 2008151702	Newron Pharmaceuticals	Preclinical

Dopamine D_3 receptor

The D_3 receptor is the longest isoform of the D_2-like receptor subfamily, all of which can not only reduce cAMP production by coupling to $G_{\alpha i/o}$ proteins, but also regulate Ca^{2+} and potassium ion channels. The D_3 receptor has been implicated in the control of drug-seeking behavior, and may play a role in the pathophysiology of impulse control disorders, bipolar disorder and schizophrenia. Studies have shown a reduction in the expression of dopamine D_3 receptor mRNA in individuals suffering from schizophrenia and bipolar disorder, suggesting a distorted homeostasis of dopamine receptor subtypes in these illnesses. D_3 modulators have shown antipsychotic properties and reverse cognitive deficits, and selective D_3 antagonists are under development for the treatment of diseases such as schizophrenia, depression, anxiety and bipolar disorder (15-17).

$GABA_A$ receptor

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and spinal cord that acts via $GABA_A$, $GABA_B$ and $GABA_C$ receptors. The $GABA_A$ receptor is widely distributed throughout the CNS. It is ionotropic and can be activated by several different compounds. It is believed to be involved in the modulation of vigilance, anxiety, muscle tension, epileptogenic activity and memory functions. Enhancement of $GABA_A$ receptor-mediated fast synaptic inhibition may be effective in improving cognition. $GABA_B$ receptors are widely distributed throughout the CNS and in peripheral autonomic terminals and are metabotropic, thereby distinguishing them from ionotropic $GABA_A$ receptors. $GABA_A$ agonists decrease catalepsy, exhibiting antischizophrenic efficacy with diminished extrapyramidal effects. $GABA_A$ modulators are also being investigated for the treatment of a wide variety of other diseases, including gastrointestinal, neurological and psychiatric conditions such as depression, anxiety and bipolar disorder (18-20).

Glycogen synthase kinase-3 (GSK-3)

The GSK-3 enzyme (EC 2.7.11.26) was originally identified as the kinase responsible for phosphorylating and inhibiting glycogen synthase, the rate-limiting enzyme of glycogen biosynthesis. Alpha and beta isoforms have been identified which have similar biochemical properties. The *GSK3* gene is ubiquitously expressed. Furthermore, GSK-3 phosphorylates β-catenin, a key mediator of the Wnt signaling pathway, and GLI proteins, which are the effectors of Hedgehog signaling. Both pathways are implicated in embryo development and in the pathogenesis of some cancers. Modulators of GSK-3 have been used as therapy for certain psychiatric diseases such as bipolar disorder and are also being studied for the treatment of cancer and neurological disorders (21-24).

5-HT_{1A} receptor

In the CNS, serotonin (5-hydroxytryptamine, 5-HT) is a biogenic amine neurotransmitter synthesized in neurons of the raphe nucleus in the brain stem and present in high concentrations in the hypothalamus and basal ganglia. The serotonergic system innervates almost all areas of the brain and spinal cord, and 5-HT is involved in a wide variety of behaviors, including affective state, sleep–wakefulness, feeding behavior, sexual behavior, temperature regulation, circadian rhythmicity, locomotion, neuroendocrine secretion, pain, hallucinogenesis and memory. 5-HT is also present in peripheral tissues and in carcinoid tumors and it is a potent vasoconstrictor released from platelets to inhibit gastric secretion and stimulate smooth muscle. The 5-HT_{1A} receptor is a GPCR component of the 5-HT system that is present both pre- and postsynaptically in different brain areas. It is G_i/G_o-coupled and acts by decreasing cellular levels of cAMP via inhibition of adenylate cyclase. The 5-HT_{1A} receptor has been implicated in the pathogenesis of Alzheimer's disease (AD) and agents targeting the receptor may be effective in the treatment of obesity and psychiatric disorders such as schizophrenia, depression, anxiety and bipolar disorder (25-27).

5-HT_{2A} receptor

The 5-HT_{2A} receptor is a GPCR (G_q/G_{11}) for 5-HT that belongs to the class of phosphoinositide-specific PLC-linked receptors that, upon activation, leads to mobilization of intracellular Ca^{2+} and activation of PKC. The 5-HT_{2A} receptor is localized in postsynaptic neurons of the limbic areas and prefrontal cortex, as a monomer, a homodimer or forming functional complexes with other proteins. Selective 5-HT_{2A} antagonists possess anticataleptic properties, suggesting that these agents could attenuate the extrapyramidal side effects observed with typical antipsychotics. For this reason, agents that combine dopamine receptor partial agonism and 5-HT_{2A} receptor antagonism are potential therapies for schizophrenia. Moreover, it is also a potential target in a variety of neuropsychological diseases such as anxiety, depression and bipolar disorder (28, 29).

L-type calcium channel

The L-type calcium channel is a large transmembrane, voltage-gated ion channel with selective permeability for Ca^{2+} ions. It is essential for neuronal signal transmission and intracellular signal transduction and is structurally related to T-type calcium channels, exhibits sustained conductance, is slowly inactivating and is regulated by cAMP-dependent protein kinase (e.g., phosphorylation enhances the probability of channel opening). It is found on skeletal, cardiac and smooth muscle cells and within the nervous system, where it is expressed on neurons and neuroendocrine cells. In the cardiovascular system, it is responsible for the plateau phase (i.e., slow inward current) of the action potential and it triggers the release of internal Ca^{2+}. It has been suggested that modulation of intracellular Ca^{2+} levels by voltage-gated calcium channels may be involved in neuronal death associated with AD and L-type calcium channel modulators have been shown to enhance cognition in AD patients. Moreover, in bipolar disorder, administration of antidepressant medications, behavioral sensitization processes and neuronal Ca^{2+} dysregulation can all lead to apoptosis of critical brain circuitry that regulates emotion. Thus, targeting dysregulation of Ca^{2+} levels in the CNS by administering L-type calcium channel blockers may have the potential for altering the cyclical course or progression of bipolar disorder (30-32).

Opioid receptors

The opioid receptors are a class of GPCRs found in regions of the brain that bind to morphine, as well as in areas that are either unrelated (e.g., striatum) or related (e.g., along the aqueduct of Sylvius) to

pain. Subtypes include μ, δ, κ and opioid-like NOP receptors, which have all been shown to have antinociceptive effects. Natural ligands for these receptors are the opiate peptide neurotransmitters (derived from proopiomelanocortin [POMC], proenkephalin, prodynorphin or pronociceptin/orphanin FQ), although opiates (e.g., morphine) are potent agonists that mimic the action of the natural transmitters. They are widely distributed in other areas of the body such as the gut. Agonists of the μ opioid receptor are used in the treatment of abdominal pain in irritable bowel syndrome and antagonists of this receptor together with levodopa may be effective in the symptomatic relief of Parkinson's disease, without eliciting dyskinesias. Delta opioid receptor agonists may be effective in ameliorating the symptoms of Parkinson's disease and κ opioid receptor agonists display neuroprotective effects against ischemic neuronal injury, suggesting that they may be an effective treatment option for stroke. Agonists at μ, δ and κ opioid receptors may be effective in the treatment of chronic pain and psychiatric diseases such as bipolar disorder (33-35).

Protein kinase C (PKC)

PKC is a family of enzymes (EC 2.7.11) that phosphorylate proteins on serine or threonine residues, usually in the presence of Ca^{2+}. PKCs are activated by membrane phospholipids that are involved in intracellular signaling. The classical PKCs (α, β_1, β_2 and γ) are Ca^{2+}-dependent and can be activated endogenously by diacylglycerol or nonphysiologically by phorbol esters; PKC may actually be the receptor protein for tumor-promoting phorbol esters. The specific physiological substrates for these enzymes are not yet known. Several Ca^{2+}-independent isoforms have also been identified. PKCγ is exclusively expressed in neurons and is involved in various neuronal functions. Among other actions, PKC regulates the intracellular trafficking of dopamine D_3 receptors in the CNS via sequestration and further desensitization by phosphorylation. The D_3 receptor is predominantly expressed in parts of the brain that control emotional behavior and its deregulation has been implicated in the pathogenesis of psychiatric diseases such as schizophrenia and bipolar disorder. Modulators of PKC may constitute an effective treatment strategy for cancer and cardiovascular, dermatological, endocrine and psychiatric conditions such as bipolar disorder (36-39).

Serotonin transporter (SERT)

The SERT is a membrane uptake carrier dependent on sodium (Na^+) and chloride (Cl^-) that transports 5-HT from the extracellular synaptic space back into 5-HT nerve terminals. SERT inhibitors increase extracellular concentrations of 5-HT and amplify signals sent by 5-HT neurons. Altered serotonergic neurotransmission and 5-HT have long been associated with psychiatric disorders, including schizophrenia and depression. Moreover, polymorphic regions in the SERT promoter and variations in its gene *5-HTTLPR* have been implicated in neuropsychiatric and mood disorders. Agents that block SERT, such as SSRIs, may be effective in the treatment of diseases characterized by altered 5-HT neurotransmission, including depression, anxiety, bipolar disorder and schizophrenia (40-42).

Sodium channel

The sodium channel is a ubiquitous, plasma membrane-bound ion channel permeable to Na^+ ions that is classified as either voltage-gated (expressed on central and peripheral neurons, skeletal muscle, cardiac myocytes) or ligand-gated (i.e., nicotinic receptors in neuromuscular junctions that bind to acetylcholine). The fast voltage-gated Na^+ channel is composed of an α and β subunit. The α subunit contains four repeat domains (I-IV), with each containing six membrane-spanning regions (S1-S6). The highly conserved S4 segment acts as the channel's voltage sensor. The channel's voltage sensitivity is mediated by positive amino acids located at every third position. When stimulated by an alteration in transmembrane voltage, this region moves toward the extracellular side of the cell membrane and the channel becomes more permeable to ions. The ions are conducted through a pore, which can be broken into two regions comprising a largely extracellular portion of "P-loops", which is responsible for ion selectivity, and the more cytoplasmic portion, formed by the combined S5 and S6 regions of the four domains. The region that links domains III and IV serves to physically plug or block the channel after extended activation, thereby inactivating it. Inhibition of voltage-gated Na^+ channels results in the stabilization of neuronal membranes and the subsequent modulation of presynaptic transmitter release of excitatory amino acids (e.g., glutamate). Na^+ channel regulation is thus important in diseases associated with neurotransmitter deregulation and Na^+ channel blockers may have potential for use in the treatment of epilepsy, pain, anxiety, angina pectoris, arrhythmia, depression and bipolar disorder (43-48).

Voltage-gated sodium channel $Na_v1.2$

$Na_v1.2$ is the α subunit of a voltage-gated Na^+ channel which is responsible for the generation and propagation of action potentials in neurons and muscle, and comprises a transmembrane glycoprotein complex with four repeat domains (I-IV), each containing six membrane-spanning regions (S1-S6); the S4 segment is the voltage sensor. It is encoded by the *SCN2A* gene, which is heterogeneously expressed in the brain, and mutations in this gene have been associated with several seizure disorders. Numerous alternatively spliced transcript variants of this gene have been reported, but the full-length nature of some of these variants has yet to be determined. Inhibition of voltage-sensitive Na^+ channels results in the stabilization of neuronal membranes and the subsequent modulation of presynaptic transmitter release of excitatory amino acids (e.g., glutamate). Na^+ channel regulation is therefore important in diseases characterized by neurotransmitter deregulation. Blockers of the α subunit may be effective in the treatment of pain, as well as neurological and psychiatric diseases such as bipolar disorder (43-48).

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