Drugs targeting ion channels

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Ion channels represent the second largest class among 435 proven effect-mediating drug targets after G-protein-coupled receptors (GPCRs) (Rask-Andersen et al., 2011). They are primary targets for therapeutic areas of neuropsychiatric disorders (such as pain, epilepsy, stroke, Alzheimer’s disease, anxiety, schizophrenia, etc.), cardiovascular and metabolic diseases (such as hypertension, arrhythmias, and diabetes), immunodiseases (such as asthma), nephrology (such as urinary retention and incontinence), irritable bowel syndrome, and pulmonary/respiratory diseases (such as chronic obstructive pulmonary airway disease). From 1939 to 2012, US Food and Drug Administration (FDA) approved a total of 2265 small molecule drugs (including the same molecular entity in different formulation) for all therapeutic areas. Among these approved drugs, there are about 730 drugs (more than one-third of the total) that have been classified as ion channel–targeting drugs although the exact mechanisms for most of them are not defined or unknown, in particular for drugs that were approved before the year of 2000. This chapter summarizes some of the representative drugs whose mechanisms of action are better studied or known. The description is organized based on target subclasses.

43.1 DRUGS ACTING ON VOLTAGE-GATED POTASSIUM CHANNELS

43.1.1 EZOGABINE OR RETIGABINE

Ezogabine (United States Adopted Name [USAN]) or Retigabine (International Nonproprietary Name [INN]) is an anticonvulsant drug used as a treatment for partial-onset seizures (Tatulian et al., 2001). This drug contains new molecular entity (NME) of N-(2-amino-4-[fluorobenzylamino]-phenyl) carbamic acid, codeveloped by Valeant and GlaxoSmithKline. It was approved by the European Medicines Agency (EMA) under the trade name Trobalt in March 2011 and by the US FDA under the trade name Potiga in June 2011.
**Mechanism of action:** Retigabine acts as a neuronal Kv7/KCNQ/M-channel opener, which is markedly different from that of other current anticonvulsants. Most anticonvulsants (such as Phenytoin, Zonisamide, and Valproate) target sodium/calcium channel and GABAA channel activity. Kv7/KCNQ channels are involved in setting the resting membrane potential and regulating neuronal activity (Jentsch et al., 2000; Wulff et al., 2009). Upregulating Kv7/KCNQ activity by retigabine repolarizes the membrane potential and inhibits repetitive firing that underlies epileptic activity. Retigabine activates four subtypes of Kv7/KCNQ channels including Kv7.2, Kv7.3, Kv7.2/7.3 and Kv7.4/7.5 channels, with an effective concentration for half maximum response (EC$_{50}$) of 1.9 µM at −30 mV for Kv7.2 (Wickenden et al., 2000; Tatulian et al., 2001; Xiong et al., 2008; Wulff et al., 2009). Its potential clinical applications include treatment of epilepsy, anxiety, neuropathic pain, and other neuropsychiatric disorders. Retigabine reaches maximum plasma concentrations between half an hour and 2 h after a single oral dose. It has a moderately high oral bioavailability (50%–60%), a high volume of distribution (6.2 L/kg), and a terminal half-life of 8–11 h (Luszczki, 2009). Retigabine is quickly absorbed and metabolized in the liver by N-glucuronidation and acetylation. Retigabine and its metabolites are excreted almost completely (84%) by kidney (Luszczki, 2009). Retigabine appears to be free of drug interactions with most commonly used anticonvulsants.

Retigabine also serves as an important chemical tool for studies of biological and pharmacological function as well as therapeutic potential of Kv7/KCNQ channel modulation.

### 43.1.2 DALFAMPRIDINE OR FAMPRIpine

Dalfampridine (USAN) or fampridine (INN) is commonly known as 4-aminopyridine (4-AP) and is widely used as a research tool compound, in characterizing subtypes of potassium channel (see Figure 43.1). It is a small molecule with the chemical formula C$_5$H$_4$N–NH$_2$. In January 2010, FDA approved dalfampridine, under the trade name Ampyra, to be used to manage some of the symptoms of multiple sclerosis (MS), and Lambert–Eaton myasthenic syndrome (LEMS).

MS is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. LEMS (sometimes named Lambert–Eaton syndrome or Eaton–Lambert syndrome) is a rare autoimmune disorder characterized by muscle weakness of the limbs. The FDA approval of Ampyra was based on two clinical trials with a total of 510 patients with MS for a period of up to 21 weeks. During the double-blind treatment period, a significantly greater proportion of patients taking Ampyra 10 mg twice daily had increases in walking speed of as much as 30% from baseline, a substantial improvement that was absent in patients taking the placebo. Spinal cord injury patients have also seen improvement with 4-AP therapy. These improvements include sensory, motor, and pulmonary functions, with a decrease in spasticity and pain.

**Mechanism of action:** 4-AP is a relatively selective blocker of members of the Kv1 family of voltage-activated potassium channels (KCNA1 gene for human homolog or Shaker for Drosophila). At concentration of 1 mM, 4-AP selectively and reversibly inhibits Shaker channels without significant effect on other sodium, calcium, and potassium conductances. Electrophysiological studies of demyelinated axons show that augmented potassium currents increase extracellular potassium ion concentration, which decreases action potential duration and amplitude, thus likely causing conduction failure. Potassium channel blockade reverses effects mediated by the increased potassium current seen in diseased neurons. Interestingly, 4-AP has also been shown as a potent calcium channel activator and it can improve synaptic and neuromuscular function by directly acting on the calcium channel beta subunit.

### 43.1.3 DRONEDARONE

Dronedarone is an antiarrhythmia drug developed by Sanofi-Aventis (see Figure 43.2). In July 2009, it was approved by the FDA under the trade name Multaq. It was recommended as an alternative to amiodarone for the treatment of atrial fibrillation (AF) and atrial flutter (AFL) in people whose heart has either returned to normal rhythm or who undergoes drug therapy or electric shock treatment to maintain normal rhythm. The FDA approval of Multaq was based on results of three studies with a total of 5865 enrolled subjects in sinus rhythm with a prior episode of AF or AFL (Hohnloser et al., 2009). The subjects were at least 75 years old, or at least 70 years old with another risk factor. They were treated for up to 30 months with either Multaq 400 mg twice daily or placebo. The time to first hospitalization for cardiovascular reasons or death from any cause was significantly decreased in the Multaq group by 24%, and the risk of cardiovascular death was reduced by 30% (Singh et al., 2007).

**Mechanism of action:** Dronedarone is considered to block the KCNH2 gene that codes for the alpha subunit of hERG (human ether-a-go-go-related gene) potassium channel, also known as Kv11.1. hERG activity mediates the rapid delayed rectifier current (I$_{Kr}$) in cardiac myocytes, responsible for the rapid phase
of repolarization of ventricular action potential. Dronedarone is a benzofuran derivative of amiodarone, an effective yet toxic antiarrhythmic drug. Unlike amiodarone, dronedarone does not contain iodine atoms and hence retains the efficacy of amiodarone without its unique toxicity profile. Dronedarone also has a much smaller volume of distribution, and has an elimination half-life of 24 h due to its less lipophilic nature, in contrast to amiodarone’s half-life of several weeks. As a result of these preferable pharmacokinetic characteristics, dronedarone dosing may be less complicated than amiodarone.

Studies also suggest that dronedarone is a multichannel blocker. It inhibits several inward potassium currents, including rapid delayed rectifier, slow delayed rectifier, and ACh-activated inward rectifier. It is also believed to reduce inward rapid Na⁺ current and current from L-type Ca²⁺ channels. The reduction in K⁺ current in some studies was shown to be due to the inhibition of K-ACH channel or associated GTP-binding proteins. Reduction of K⁺ current by 69% led to increased action potential duration and increased effective refractory period, thus has been shown to suppress pacemaker potential of the sinoatrial (SA) node and return patients to a normal heart rhythm.

43.1.4 DOFETILIDE

Dofetilide is a potent and selective class III antiarrhythmic agent for the maintenance of normal sinus rhythm in patients with AF and AFL (see Figure 43.3). Dofetilide was approved by FDA in October 1999, and is marketed under the trade name Tikosyn by Pfizer. Dofetilide is for patients with AF/AFL of greater than 1-week duration. After taking the drug, patients have been converted to normal sinus rhythm. Dofetilide is also indicated for the conversion of AF and AFL to normal sinus rhythm.

Mechanism of action: Dofetilide works by selectively blocking the rapid component of the delayed rectifier outward potassium current (I_Kr) encoded primarily by hERG and therefore increasing the effective refractory period and action potential duration without affecting the fast inward sodium current. Dofetilide has also been shown to block potassium currents such as Kv2.1 encoded by KCNK2 gene and Kir2.2 encoded by KCNJ12 gene. Kv2.1 is a member of the two-pore-domain background potassium channel family, and Kir2.2 is an ATP-sensitive inward rectifier potassium channel. The pharmacokinetic profile of dofetilide in both healthy volunteers and patients includes a linear dose–plasma concentration relationship. The terminal plasma elimination half-life is approximately 9–10 h, and systemic bioavailability is in the region of 100% (Rasmussen et al., 1992).

![Figure 43.3 Molecular structure of dofetilide, a class III antiarrhythmic agent for the maintenance of normal sinus rhythm in patients with AF and AFL.](image-url)

43.2 Drugs acting on ATP-sensitive inward rectifier K⁺ channels

43.2.1 NATEGLINIDE

Nateglinide (INN) is an antidiabetic drug for treatment of type 2 diabetes mellitus (T2DM) (see Figure 43.4). Developed by Ajinomoto company, Nateglinide was approved by FDA in 2000 and marketed under the trade name Starlix by Novartis.

Type 2 diabetes occurs due to impaired insulin secretion that becomes chronic and progressive, resulting initially in impaired glucose tolerance and eventually in type 2 diabetes. As most patients with type 2 diabetes have both insulin resistance and insulin deficiency, therapy for T2DM is aimed at controlling not only fasting, but also postprandial plasma glucose levels (Tentolouris et al., 2007).

Mechanism of action: Nateglinide, an amino acid d-phenylalanine derivative, belongs to the meglitinide class of blood glucose–lowering medications. It acts by inhibiting ATP-sensitive K⁺ channel (K_ATP channel) potassium channels in the membrane of β-cells. Inhibition of K_ATP channel activity depolarizes β-cells and causes voltage-gated calcium channels to open. The resulting calcium influx induces fusion of insulin-containing vesicles with the cell membrane, and insulin secretion occurs from the pancreas. Nateglinide restores postprandial early phase insulin secretion in a transient and glucose-sensitive manner without affecting the basal insulin level by directly acting on the pancreatic beta-cells to stimulate insulin secretion.

43.2.2 REPAGLINIDE

Repaglinide is an orally administered antidiabetic drug in the class of medications known as meglitinides that can be used to manage meal-related glucose loads (see Figure 43.5). It was approved by FDA in December 1997. Repaglinide is marketed by Novo Nordisk under the trade name Prandin in the United States, GlucoNorm in Canada, Surepost in Japan, and NovoNorm in the rest of the world.

![Figure 43.4 Molecular structure of nateglinide, an antidiabetic drug for treatment of T2DM.](image-url)

![Figure 43.5 Molecular structure of repaglinide, an orally administered antidiabetic drug, among the meglitinides which are used to manage meal-related glucose loads.](image-url)
Prandin’s quick onset and short duration of action concentrates its effect around meal time glucose load, which is important to the treatment of type 2 diabetes. Prandin is minimally excreted by the kidney, which may be an advantage for patients who suffer from decreased kidney function. Prandin posts a low risk of hypoglycemia and potentially low risk of significant weight gain.

**Mechanism of action:** Prandin lowers blood glucose by stimulating the release of insulin from the pancreas. This is achieved by closing ATP-dependent potassium channels in the membrane of the $\beta$-cells. Closing the channel depolarizes $\beta$ cell membrane, leading to opening of voltage-dependent calcium channels. The resulting calcium influx induces insulin secretion.

### 43.3.2 Chlorothiazide

Chlorothiazide (Diuril) is a thiazide diuretic and antihypertensive agent. It is used to treat fluid retention (edema) in patients with non-insulin-dependent T2DM.

**Mechanism of drug action:** Chlorothiazide works by blocking potassium large conductance calcium-activated (or big potassium, BK channels) channel alpha subunit encoded by $\text{KCNMA1}$ gene, previously known as SLO1 or Maxi-K. BK channels are activated by changes of membrane potential and/or increases of intracellular calcium. BK channels, as an attractive drug target, play a pivotal and specific role in many pathophysiological conditions including the regulation of smooth muscle tone and neuronal excitability. Chlorothiazide is not metabolized but is eliminated rapidly by the kidney with plasma half-life about 45–120 min. Chlorothiazide crosses the placental but not the blood–brain barrier.

### 43.3.3 Chlorzoxazone

Chlorzoxazone is approved by FDA also before 1982 and is sold under the trade name Muscol (see Figure 43.8). Chlorzoxazone is a centrally acting muscle relaxant. It is used to treat muscle spasm and the resulting pain or discomfort.

**Mechanism of drug action:** As an activator of $\text{Ca}^{2+}$-dependent $K^+$ channels ($I_{\text{KCa}}$), chlorzoxazone reversibly increases the channel current in a concentration-dependent manner with an EC$_{50}$ value of 30 $\mu$M (Cao et al., 2001; Liu et al., 2003). The chlorzoxazone-stimulated $I_{\text{KCa}}$ was inhibited by iberitoxin (200 nM) or clotrimazole (10 $\mu$M), but not by glibenclamide (10 $\mu$M) or apamin (200 nM). Chlorzoxazone (30 $\mu$M) suppressed voltage-dependent L-type $\text{Ca}^{2+}$ current. In the inside-out configuration, chlorzoxazone applied to the intracellular side of the patch did not modify single-channel conductance of large conductance $\text{Ca}^{2+}$-activated $K^+$ channels (BK), but did increase channel activity by increasing the mean open time and decreasing the mean closed time. Chlorzoxazone also caused a left shift in the activation curve of BK channels, which promotes channel opening under physiological conditions. The $\text{Ca}^{2+}$ sensitivity of these channels was unaffected by chlorzoxazone. Under current-clamp condition, chlorzoxazone (10 $\mu$M) reduced the firing rate of action potentials.
43.4 DRUGS ACTING ON VOLTAGE-GATED \( \text{Na}^+ \) CHANNELS

### 43.4.1 RANOLAZINE

Ranolazine (Ranexa) is an oral anti-ischemic/anti-anginal drug, designed to act without reducing heart rate or blood pressure (see Figure 43.9). It was developed by CV Therapeutics and approved under the trade name Ranexa by FDA in January 2006.

Ranexa is specifically a useful new option for patients with myocardial ischemia and chronic stable angina whose symptoms are not controlled with first-line anti-anginal therapy or who do not tolerate first-line anti-anginal agents. Approval of Ranexa was based on a pair of clinical trials, dubbed ERICA (Efficacy of Ranolazine In Chronic Angina) and CARISA (Combination Assessment of Ranolazine In Stable Angina). In general, myocardial ischemia is associated with reduced adenosine triphosphate fluxes and decreased energy supply, resulting in severe disturbances of intracellular ion homeostasis in cardiac myocytes. Experimental and clinical studies have shown that ranolazine is effective in reducing manifestations of ischemia and angina, and it also holds potential promise to be effective in the management of left ventricular dysfunction, particularly diastolic dysfunction, and arrhythmias (Stone, 2008; Maier, 2009; Reffelmann and Kloner, 2010). In the ventricles, ranolazine can suppress arrhythmias associated with acute coronary syndrome, long QT syndrome, heart failure, ischemia, and reperfusion. In atria, ranolazine effectively suppresses atrial tachyarrhythmias and AF.

**Mechanism of drug action:** Ranolazine’s mechanism of action has not been fully characterized. The drug has been shown to exert its anti-anginal and anti-ischemic effects without reducing heart rate or blood pressure. Ranolazine, a specific inhibitor of late I(\( \text{Na} \)), reduces Na\(^{+} \) influx and hence ameliorates disturbed Na\(^{+} \) and Ca\(^{2+} \) homeostasis. The principal mechanism underlying ranolazine’s antiarrhythmic actions is thought to be primarily via inhibition of the persistent or late I(\( \text{Na} \)) in the ventricles and via use-dependent inhibition of peak I(\( \text{Na} \)) and I(Kr) in the atria. Short- and long-term safety of ranolazine has been demonstrated in the clinic, even in patients with structural heart disease (Antzelevitch et al., 2011). Ranolazine also affects the sodium-dependent calcium channels during myocardial ischemia in rabbits by altering the intracellular sodium level. Thus, ranolazine indirectly prevents the calcium overload that causes cardiac ischemia in rats. The effects of ranolazine on the Na, 1.7 and Na, 1.8 sodium channels also make it potentially useful in the treatment of neuropathic pain (Casey et al., 2010).

![Figure 43.9](image_url) Molecular structure of ranolazine (Ranexa), an oral anti-ischemic/anti-anginal drug designed to act without reducing heart rate or blood pressure.

### 43.4.2 OXCARBAZEPINE

Oxcarbazepine is an anticonvulsant or antiepileptic drug (AED), used primarily in the treatment of partial seizures in adults with epilepsy and for the adjunctive treatment of partial seizures in children, aged 4–16, with epilepsy (see Figure 43.10). Oxcarbazepine is marketed as Trileptal by Novartis and approved by FDA in January 2000.

**Mechanism of drug action:** The precise mechanism by which oxcarbazepine exerts antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in the stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. In addition, increased potassium conduction and modulation of high-voltage-activated calcium channels may contribute to the anticonvulsive effects of the drug.

### 43.5 DRUGS ACTING ON VOLTAGE-GATED \( \text{Ca}^{2+} \) CHANNELS

#### 43.5.1 CLEVIDIPINE

Cleviprex (INN) was developed by The Medicines Company for the treatment of hypertension and was approved under the trade name Cleviprex by FDA in August 2008 (see Figure 43.11). Cleviprex is indicated for the reduction of blood pressure, acting by selectively relaxing smooth muscle cells that line small arteries. This results in widening of the arterial lumen and reduction of blood pressure since the small arterioles are the primary resistance vessel within the vasculature.

**Mechanism of action:** Cleviprex is an intravenous short-acting dihydropyridine L-type calcium channel blocker, highly selective for vascular, as opposed to myocardial, smooth muscle and, therefore, has little or no effect on myocardial contractility or cardiac conduction. It reduces mean arterial blood pressure by decreasing systemic vascular resistance. Cleviprex does not reduce cardiac filling pressure (pre-load), confirming lack of effects on cardiac output.

![Figure 43.10](image_url) Molecular structure of oxcarbazepine, an anticonvulsant or AED used primarily in the treatment of partial seizures.

![Figure 43.11](image_url) Molecular structure of clevidipine, a drug used to treat hypertension.
the venous capacitance vessels. No increase in myocardial lactate production in coronary sinus blood has been seen, confirming the absence of myocardial ischemia due to coronary steal.

43.5.2 PREGABALIN

Pregabalin (INN) (Lyrica) is an anticonvulsant drug used for neuropathic pain that was approved by FDA in December 2004 (see Figure 43.12). Pregabalin was marketed by Pfizer under the trade name Lyrica. It has also been found effective for generalized anxiety disorder and was approved for this use in the European Union (EU) in 2007. In addition, Pregabalin is also used off-label for the treatment of chronic pain, post-herpetic neuralgia (PHN), diabetic peripheral neuropathy and fibromyalgia, perioperative pain, and migraine. Pregabalin (Lyrica) was approved by FDA in June 2012 for the treatment of neuropathic pain associated with spinal cord injury.

Mechanism of action: Lyrica (pregabalin) is a modulator of voltage-gated calcium channels, designed to affect neurological transmission in multiple systems. The exact mechanism of Lyrica’s action has not been fully characterized. Lyrica binds to the alpha2-delta auxiliary subunit of voltage-gated calcium channels. Blockade of these channels has been shown to inhibit the calcium-dependent release of a number of neurotransmitters. The drug is a structural derivative of the inhibitory neurotransmitter \(\gamma\)-Aminobutyric acid (GABA), though it does not bind directly to GABAa, GABAb, or benzodiazepine receptors, does not augment GABAa responses in cultured neurons, does not alter rat brain GABA concentration, or have acute effects on GABA uptake or degradation. In cultured neurons, prolonged application of pregabalin increased the density of GABA transporter protein and increased the rate of functional GABA transport. The drug does not achieve its antinociceptive or antiseizure activity through blockade of sodium channels, activation of opioid receptors, alteration of cyclooxygenase enzyme activity, through activity at serotonin and dopamine receptors, or through effect on dopamine, serotonin, or noradrenaline reuptake.

43.5.3 GABAPENTIN

Gabapentin is an anticonvulsant previously approved by FDA in March 2000 and marketed by Pfizer under the trade name Neurontin as an adjunct treatment for partial epileptic seizures in adults and children (see Figure 43.13). In October 2000, Neurontin in oral solution was also approved as an adjunctive therapy in the treatment of partial seizures in pediatric patients 3 years of age and older. In May 2002, FDA approved Neurontin again for the management of PHN. Neurontin is the first oral medication approved by the FDA for this indication.

Gabapentin enacarbil, as an extended-release formulation of gabapentin, was approved for the treatment of restless leg syndrome by FDA in April 2011 under the trade name Horizant developed by GSK. Gabapentin enacarbil is also approved by FDA in June 2012 for the treatment of PHN under the trade name Horizant developed by GSK. The FDA approval of Horizant for PHN was based on the results of one 12-week clinical trial in total of 279 adult subjects that are divided in three dosing groups. Treatment with Horizant statistically significantly improved the mean pain score and increased the proportion of subjects with at least a 50% reduction in pain score from baseline at all doses tested. A benefit over placebo was observed for all 3 doses of Horizant (1200, 2400, and 3600 mg/day) as early as week 1 and maintained to the end of treatment.

Mechanism of action: How Gabapentin works remains elusive, but it was considered to block voltage-gated calcium channels. Gabapentin was designed as a lipophilic GABA analog and was first synthesized as a potential anticonvulsant and was launched in 1994 as an add-on therapy for the treatment of epilepsy (Bryans and Wustrow, 1999). More recent studies suggest \(\alpha/2/\delta\) auxiliary subunit of voltage-gated calcium channels serves as the target for this drug’s actions (Maneuf et al., 2006; Thorpe and Offord, 2010).

43.6 DRUGS ACTING ON TRANSIENT RECEPTOR POTENTIAL (TRP) CHANNELS

43.6.1 CAPSAICIN

Capsaicin is the active component of chili peppers and produces a sensation of burning in tissues with which it comes into contact (see Figure 43.14). Capsaicin (\(C_{18}H_{27}NO_3\)) is currently used in a high-dose dermal patch that was developed by a company called NeurogesX and was approved by FDA in 2009 under the trade name Qutenza for neuropathic pain associated with PHN caused by shingles (Backonja et al., 2008; Babbar et al., 2009).

Qutenza (capsaicin) 8% is a transdermal patch containing capsaicin in a localized dermal delivery system. The capsaicin in Qutenza is a synthetic equivalent of the naturally occurring compound found in chili peppers. Qutenza works by targeting certain pain nerves in the area of skin where pain is being experienced.

Mechanism of action: Capsaicin selectively binds to TRPV1 that resides on the membranes of nociceptive and heat-sensing neurons, permitting cations to pass through the cell membrane and into the cell. The resulting depolarization of the neuron signals to the brain. TRPV1 is a heat-activated calcium-permeable

![Molecular structure of pregabalin](image1.png)

![Molecular structure of gabapentin](image2.png)

![Molecular structure of capsaicin](image3.png)
nonselective cation channel that was cloned in 1997 (Caterina et al., 1997). TRPV1 opens when temperature reaches at or above 43°C. When capsaicin binds to TRPV1, it activates the channel to open below 37°C, causing the sensation of heat. Prolonged activation of these neurons by capsaicin depletes presynaptic substance P, one of the body’s neurotransmitters for pain and heat.

43.6.2 MENTHOL

Menthol is a natural compound synthesized or extracted from cornmint and peppermint with chemical molecular formula of C_{10}H_{13}O (see Figure 43.15). Menthol, a monoterpenic widely used in cosmetics and as a flavoring agent, was approved as antipruritics, also known as ant-itch drugs, by FDA before 1982 for use of inhibiting itching that is often associated with sunburns, allergic reactions, eczema, psoriasis, chickenpox, fungal infections, insect bites and stings, and contact dermatitis.

Mechanism of action: Menthol acts upon TRP channels by rapidly increasing intracellular calcium and mobilizing calcium flux through the channels. Menthol’s characteristic well-known cooling sensation is due to the activation of TRP melastatin family member 8 (TRPM8) channels expressed in sensory neurons and the skin when inhaled, eaten, or applied to the skin. TRPM8 is activated when temperatures drop at or below 28°C. Application of menthol to dorsal root ganglia (DRG) neurons results in a rapid increase in intracellular calcium at the presynaptic terminals from intracellular calcium store (Tsuzuki et al., 2004). The calcium influx caused by menthol activity within the presynaptic sites acts as a mediator for release of glutamate for enhanced glutamatergic and glycinergic neurotransmission at sensory synapses, resulting in cold sensation and analgesia (Tsuzuki et al., 2004).

It has been proposed that the specific interaction with two cysteine residues (C929 and C940) between transmembrane segments 5 and 6 may point to a menthol-specific interaction with the receptor, whereas binding to the transmembrane segment 2 and the carboxyl terminus refers to a preserved general binding site for modulators of the receptor. This would explain the differences in responses to the cold-sensitizing agent ilicin and menthol (Farco and Grundmann, 2013).

Menthol also activates TRP subfamily A member 1 (TRPA1) and modulates the channel to increase intracellular calcium. However, the modulation appears to be bimodal with activation of mouse TRPA1 receptor at low concentrations but inhibition of the receptor at high concentrations (Xiao et al., 2008). The pore region and transmembrane segments 5 and 6 of TRPA1 are critical for menthol responsiveness (Xiao et al., 2008). Aside from its cold-inducing sensation capabilities, menthol exhibits cytotoxic effects in cancer cells, induces reduction in malignant cell growth, engages in synergistic excitation of GABA receptors, and inhibits Na$_{1.8}$ and Na$_{1.9}$ as well as nicotinic acetylcholine receptors.

43.7 DRUGS ACTING ON NEURONAL ACETYLCHOLINE RECEPTOR SUBUNIT ALPHA-7

Varenicline (C$_{13}$H$_{13}$N$_2$) was discovered and marketed by Pfizer under the trade name Champix in the United States and Champix in Canada, Europe, and other countries (see Figure 43.16). Varenicline was approved by FDA and EU in 2006 for smoking cessation. Varenicline functions as nicotinic receptor partial agonist as it stimulates nicotine receptors more weakly than nicotine itself does. As a partial agonist, it reduces cravings for and decreases the pleasurable effects of cigarettes and other tobacco products, the mechanisms by which varenicline can assist some patients to quit smoking (Jorenby et al., 2006).

Mechanism of drug action: Varenicline is a full agonist on α7 receptors, but it is a partial agonist of the α3β2 subtype of nicotinic acetylcholine receptor (Mihalak et al., 2006). Acting as a partial agonist, varenicline binds to α3β2 and partially stimulates the receptor without producing a full effect like nicotine. Varenicline also acts as an agonist at 5-HT3 receptors, which may contribute to mood-altering effects of varenicline. In addition, it acts on α3β4- and weakly on α3β2- and α6-containing receptors (Mihalak et al., 2006).

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