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# Potassium Channel Modifiers: A Review.

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**ABSTRACT**

Ion channel pharmacology is important aspect of drug research as many drugs acts by modulating these channels. Among these ion channels, potassium channels are very important as a newer target for various diseases. It is important to know the structures and types of ion channels to have through knowledge about drug targets. There are various drugs which acts by modulating or modifying $K^+$ channels that include opener drugs, blockers drugs and various toxins. Apart from Minoxidil various next generation drugs have developed as openers with wide range of indications. Blockers of $K^+$ channels include antiarrhythmic drugs, anti-diabetic agents and few other classes of drugs. In this simple review we have described an overview of K+ channel structure and function and drugs that act by modulating these channels, their uses and current status.

**Keywords**: Potassium channels, Potassium channel modifiers, ion channel Pharmacology, Potassium channel openers, Potassium channel blockers, drugs acting on Potassium channels.

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## INTRODUCTION

Ions are charged particles e.g. $Na^{+,}$ $H^{+}$, $K^{+}$ and $Cl^{-}$. Ions have a significant effect on many cell functions and they influence the amount of water in the cell. Cells use inorganic ions for transmitting signals across the cell membrane or along the surface of the cell. Other cellular functions as diverse as secretion of hormones to fertilization of egg cells require ion transport across the cell membrane [1].

Ion channels are involved in various cellular functions as well as in causing channelopathies. Various drugs that act by modulating ion channels are important research tool for the scientists which are involved in various pathologies. Ion channel modulators have been in use since long time. Ion channel function is modulated by many natural agents of the animal and plant kingdoms contributing the dangerous effects of poisons or the beneficial effects of medicinal herbs. Once isolated, these lead compounds have served as the basis for the synthesis of more specific ligands with fewer side effects. For instance, cocaine extracted from coca leaves entered clinical practice in the 1880s for its analgesic properties, but the occurrence of CNS and cardiovascular toxicity led medicinal chemists to synthesize new derivatives, thus giving rise to the pharmaceutical class of local anesthetics, which are selective blockers of sodium channels [2]. Beyond their usefulness in the clinical setting, natural ion channel ligands, especially toxins with high binding affinity, have also largely contributed to the discovery of the various ion channels and the understanding of their structure and function long before their molecular identification.

**Classification of Ion Channels** [3].

Ion channels are classified as voltage gated and ligand gated channels depending on gating.

**Table 1: Classification of ion channels**

| **Voltage-gated ion channel** |
|---|
| Voltage-gated sodium channels |
| Voltage-gated calcium channels<br>Voltage-gated potassium channels (KV) |
| Cation channels of sperm |
| Voltage-gated proton channels |
| **Ligand-gated ion channel** |
| Cys-loop receptors: GABAA, Glycine, Seroton |
| Ionotropic glutamate receptors: AMPA, Kainate, NMDA |
| ATP-gated channels: P2X |

On the basis of Species of Ions passing through the gates ion channels are classified into Chloride channels, Potassium channels, Calcium-activated potassium channels, Inward-rectifier potassium channels, Two-pore-domain potassium channels, Sodium channels, Voltage-gated sodium channels, Epithelial sodium channels, Calcium channels, Proton channels, Voltage-gated proton channel etc. Depending on number of pores on channels are classified into Single pore channels and two-pore channels. Most of ion channels are of single pore type.

**Structure of Potassium Channel**

There are four major classes of potassium channels: Calcium-activated potassium channel - open in response to the presence of calcium ions or other signalling molecules. Inwardly rectifying potassium channel - passes current (positive charge) more easily in the inward direction (into the cell). Tandem pore domain potassium channel - are constitutively open or possess high basal activation, such as the "resting potassium channels" or "leak channels" that set the negative membrane potential of neurons. Voltage-gated potassium channel - are voltage-gated ion channels that open or close in response to changes in the transmembrane voltage. Structure and types of $K^{+}$ channels is shown in figure 1.

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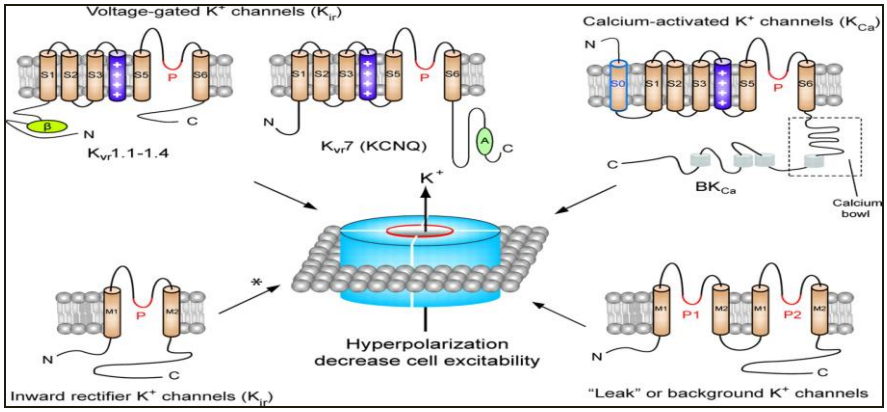


**Figure 1: Structure of potassium channel**

**Potassium Channel Classes, Function, and Pharmacology**

Table 2 provides the information about types of $K^+$ channels, their subclasses, functions, blockers and activators [4].

**Table 2: $K^+$ channels- an overview**

| Class | Subclasses | Function | Blockers | Activators |
|---|---|---|---|---|
| Calcium activated<br>6T & 1P | BK channel<br>SK channel<br>IK channel | inhibition in response to rising intracellular calcium | charybdotoxin, iberiotoxin<br>apamin | 1-EBIO<br>NS309<br>CyPPA |
| Inwardly rectifying<br>2T & 1P | ROMK (Kir1.1) | recycling and secretion of potassium in nephrons | Nonselective: Ba2+, Cs+ | none |
| | GPCR regulated (Kir3.x) | mediate the inhibitory effect of many GPCRs | GPCR antagonists<br>ifenprodil | GPCR agonists |
| | ATP-sensitive (Kir6.x) | close when ATP is high to promote insulin secretion | glibenclamide<br>tolbutamide | diazoxide<br>pinacidil<br>minoxidil<br>nicorandil |
| Tandem Pore domain<br>4T & 2P | TWIK (TWIK-1, TWIK-2, KCNK7)<br>TREK (TREK-1, TREK-2, TRAAK<br>TASK (TASK-1, TASK-3, TASK-5) TALK (TASK-2, TALK-1, TALK-2)<br>THIK (THIK-1, THIK-2)<br>TRESK | Contribute to resting membrane potential | Bupivacaine<br>quinidine | halothane |
| Voltage gated<br>6T & 1P | hERG (Kv11.1)<br>KvLQT1 (Kv7.1) | action potential repolarization limits frequency of action potentials (disturbances Cause dysrhythmia) | tetraethylammonium<br>4-aminopyridine<br>dendrotoxins (some types) | retigabine (Kv7) |

**$K^+$ Channel Modifiers**

Various drugs act by modifying the $K^+$ channels by either opening or blocking them. Some toxins also act on these channels and show wide range of toxicities.
$K^+$ channel openers:

**Minoxidil**

Active Molecule of Minoxidil is Minoxidil N-O sulphate. This drug activates the ATP sensitive $K^+$ channels & causes relaxation of vascular smooth muscles. This drug is mainly used for treating male pattern baldness and sometimes to treat severe and drug resistant hypertension. It recruits telogen follicles into anagen and then producing a longer hair by increasing the length of the actively growing phase of the anagen hair cycle. 5% conc. for men and a 2% conc. for women are usually used. It is more effective in younger men and central balding. Adverse effects include Hypertrichosis, Salt & water retention, increased heart rate and myocardial contractility and $O_2$ consumption [5].

**Diazoxide**

It opens ATP sensitive potassium channels causing relaxation of vascular smooth muscles. Diazoxide is an arteriolar dilator. It is used to treat hypertension and insulinoma. Excessive hypotension may lead to stroke or Myocardial infarction. Reflex sympathetic response may cause angina, Myocardial infarction, cardiac failure [6].

**Nicorandil**

It relaxes vascular smooth muscles. It also enhances cardiac endothelial nitric oxide synthase expression. It has got anti-platelet, Fibrinolytic and Anti-oxidant properties. Nicorandil is involved in myocardial protection through cardiac KATP channels. It is used to treat angina pectoris [7].

**Pinacidil**

It is orally administered dug causing activation of KATP channels. It causes peripheral vasodilatation &decreases Blood pressure without significant direct effects on cardiac electrophysiology. Pinacidil is indicated in essential hypertension. Side effects of Pinacidil include headache, oedema, palpitations and tachycardia. This drug is usually given along with a diuretic.

**Cromakalim & Analogues**

These group of drugs act on KATP channels. Examples include Cromakalim, Levcromakalim, Bimakalim, Aprikalim, Iptakalim, Rilmakalim. These are potent vasorelaxants, so can be used in hypertension. They cause bronchodilatation and reduces inflammation. They also have anti-ulcer & cardioprotectant and Neuroprotectant action. They also possess myorelaxant activity in the bladder [8].

**Retigabine/ ezogabine**

This is an anticonvulsant drug which is approved by FDA in June 10, 2010. Retigabine is neuronal KCNQ/Kv7 potassium channel opener. This drug showed suppressed seizures activity in all the animal models by acting on voltage gated potassium channels in the brain. It is being investigated for other uses also like migraine, neuropathic pain and post-herpetic neuralgia. Common adverse effects include drowsiness, dizziness, vertigo, confusion and slurred speech. In 2013 FDA warned the public that, Retigabine can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina [9].

**Levosimendan**

It is calcium sensitizer causing positive inotropic effect in myocytes. It is vasodilator too and acts through ATP sensitive potassium channels. It has cardioprotective action. Indication of this drug include

inotropic support in acutely decompensated CHF. Adverse effects are headache, nausea, hypotension & arrhythmias.

**Riluzole**

This drug acts on calcium activated potassium channels i.e. SK channel opener. It is an anti-glutamate agent used orally. Caution is required with impaired renal and/or hepatic function. It is used in Amyotrophic lateral sclerosis 50 mg every 12 hours (FDA approved). It is not indicated less than 18 years. Adverse effects include abdominal pain with Cramps, Anorexia, diarrhoea, dizziness. Riluzole is under Phase II trial for symptomatic approach in patients with chronic cerebellar ataxia [10].

Potassium Channel Blockers:

**Antiarrhythmics – class III** [11]

**Amiodarone**

It blocks voltage gated (rapid current) & prolongs action potential duration. It also block slow current (Iks) on chronic administration and blocks the inactivated $Na^{++}$ channels, weak adrenergic and $Ca^{++}$ channel blocking action. It has all class properties – I, II, III & IV. Main uses of Amiodarone include acute life threatening arrhythmia as well as in chronic suppression of arrhythmias, refractory ventricular fibrillation.

**Dronedarone**

It is a derivative of Amiodarone with iodine moieties removed. This is first antiarrhythmic to demonstrate a reduction in mortality or hospitalization in patients with atrial fibrillation. January 14, 2011 - FDA notified about rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant.

**Dofetilide**

It selectively blocks the IKr i.e. “pure IKr blocker” with 100% bioavailability. It restores and maintains sinus rhythm in atrial fibrillation and flutter. But it causes dose dependant increase in QT interval. It can cause Torsade's. [12]

**Ibutilide**

It acts by blockade of IKr and activates the slow inward $Na^{++}$ current. It is used intravenously for acute conversion of atrial fibrillation or atrial flutter to sinus rhythm. It is more effective in atrial flutter. Most imp side effect is QT prolongation & Torsade’s.

**Sotalol**

It is nonselective β blocker & it also prolongs action potential duration by inhibiting the delayed rectifier and possibly other $K^{+}$ currents. It has class II & III actions. Main uses include life threatening ventricular arrhythmias, maintenance of sinus rhythm in atrial fibrillation. In 2014 FDA has approved Sotalol hydrochloride oral solution for the treatment of documented life-threatening ventricular arrhythmias and the maintenance of normal sinus rhythm in patients with a history of highly symptomatic atrial fibrillation/flutter [13].

**Vernakalant**

It is a multichannel blocker. It prolongs atrial effective refractory period and slows conduction over AV node.it doesn’t cause change in QT interval. It is effective in effective in converting recent-onset atrial fibrillation to normal sinus rhythm [14].

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**Nifekalant**

It mainly block the rapid delayed rectifier K+ current. It is used in ventricular tachycardia and fibrillation. This drug is approved in Japan. Other drugs which are at investigational stage are Azimilide, Tedisamil, Bunaftine, E-4031.

**Anti-diabetics**

These include the insulin secretragogues that are sulphonylureas and Meglitinides. They block the ATP sensitive potassium channels on the β cells of the pancreas & inhibit the efflux of potassium which causes the electric potential over the membrane to become more positive. This depolarisation open voltage gated $Ca^{++}$ channels which in turn results in increased secretion of insulin.Examples of sulfonylureas are shown in the table 3.

**Table 3: sulfonylureas**

| 1st Generation | 2nd Generation | 3rdGeneration |
|---|---|---|
| Acetohexamide<br>Chlorpropamide<br>Tolbutamide<br>Tolazamide | Glipizide<br>Gliclazide<br>Glibenclamide<br>Gliquidone<br>Glycopyramide | Glimepiride |

**Meglitinides**

These include Repaglinide, Nateglinide, Mitiglinide. These are exclusively used in Type 2 diabetes. Side effect include hypoglycemia and weight gain.

**Dalfampridine (ampyra)**

This is broad spectrum potassium channel blocker which Increases the conduction of action potentials in demyelinated axons through inhibition of potassium channels. Ampyra is indicated to improve walking in patients with multiple sclerosis as it increases walking speed. Adverse effects of it include urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain [15].

**Toxins**

There are various toxins which acts by blocking the functions of K+ channels and causes toxicities. All these are listed in the Table 4.

**Table 4: Toxins that act by blockade of K+ channels: [16, 17]**

| Toxin | Source | Channel blocked | Toxicity | Remark |
|---|---|---|---|---|
| Dendrotoxin | Mamba snakes (dendroaspis) | Voltage gated | Hyper- Excitability & convulsions | Used to study $K^+$ channels |
| Iberiotoxin | Eastern Indian Red Scorpion (Buthus Tamulus) | Calcium activated (BK) | Cardio-Pulmonary abnormality | Treat pain, hypovolemia, HTN |
| Charybdotoxin | Scorpion (Leiurus hebraeus) | Calcium activated | Neuronal hyper-excitability | Treatment by anti-Scorpion venom serum |
| Apamin | Western honey bee (Apis Mellifera) | Calcium Activated (SK) | CNS & Cardiac abnormalities | Treatment by anti-inflammatory, antihistamines, prednisolone |
| Margatoxin | Scorpion (Centruroides margaritatus) | Voltage gated | Anaphylactic reaction | Symptomatic treatment |
| Maurotoxin | Scorpion (Scorpio Maurus Palmatus) | Voltage & Calcium activated (SK,IK) | - | Used to study $K^+$ channels |
| Scyllatoxin | Scorpion (Leiurus hebraeus) | Calcium activated | Muscle hyper-contractility | - |
| Tamapin | Indian Red Scorpion (Mesobuthus tamalus) | Calcium activated (SK) | CNS & Cardiac abnormalities | - |

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**Newer Drugs & Theories**

Explosive amount of research amount of research is required in the field of ion channel pharmacology. Channel selective drugsof drugs is important concept as it increases the efficacy and reduces the side effects. There are various new drugs which are in the pipeline and undergoing the initial testing. And various existing drugs having effect on potassium channels have been under trial for newer indications. Table 5 and 6 provides information about these drugswhich either activates or blocks the the K+ channels.

**Table 5: Activators of $K^+$ channels with new features**

| DRUGS | CHANNEL | EFFECTS & USE |
|---|---|---|
| BMS-204352<br>Riluzole | Calcium activated ($B_{KCa}$) | Reduces excitability & provides neuroprotection,used in stroke,ataxia,epilepsy |
| NS-309 | Calcium activated ($S_{KCa}$) | Relaxant activity in bladder, can be used in detrusor hyperactivity |
| Chlorzoxazone [18] | Potassium channels (SK)<br>Calcium activated ($I_{KCa}$) | Reduces tremors & convulsions |
| Ciglitazone | Calcium activated ($I_{KCa}$) | Prevention of progressive cavitation in spinal cord injury |
| Volatile & Local Anaesthetics | Two pore domain | Hyperpolarization in brain stem neurons, immobilizing & sedative effects. |

**Table 6: Blockers of $K^+$ channels with new features**

| DRUGS | CHANNEL | EFFECTS & USE |
|---|---|---|
| Cromanol-293B [19]<br>L-7358211<br>HMR-1556 | Voltage gated<br>(selective $I_{Ks}$) | Used in arrhythmia. Less incidence of Torsades which is mainly d/t $I_{Kr}$ |
| Linopiridine<br>XE-991<br>Apamin | Voltage gated | ↑ NT release in the brain, Cognition & memory enhancer |
| UK-78282<br>WIN-17317-3 | Voltage gated<br>(Selective Kv 1.3) | Present on T lymphocytes, possible role in immonosuppression |
| TRAM 34 | Calcium activated | Immunosupression, can be used in RA, transplant, Asthma, PBC |
| ICA-17043<br>Cetiedil | Calcium activated<br>($IK_{Ca}$) | Blocks sickling pathway, used in SCA & β thalassemia |
| Ketoconazole<br>Econazole | Calcium activated ($BK_{Ca}$) | Sickle cell anemia & β thalassemia |
| Clotrimazole | Calcium activated<br>($IK_{Ca}$) | Reduces $Cl^-$ secretion in the colon, can be used in secretory diarrhea |

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