# Receptor-regulated ion channels

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Recent advances in the study of receptor-regulated ion channels include the cloning of the genes encoding three types of potassium channel that are favorite targets of receptors for transmitters and hormones. Studies of these channels have also provided a strong indication that G-protein βγ subunits may gate ion channels via direct protein–protein interactions. Similarities between channel regulation by natriuretic peptides and channel regulation by secreted peptide products of the Alzheimer's β-amyloid precursor protein offer hints for the existence of a receptor for the latter. There are also other novel examples of channel regulation in excitable and nonexcitable cells, including liver cells and blood cells.

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Abbreviations

| | |
|---|---|
| β-APP | β-amyloid precursor protein |
| ABC | ATP-binding cassette |
| ANP | atrial natriuretic peptide |
| BK | large-conductance $Ca^{2+}$-activated $K^+$ channel |
| $GABA_B$ | γ-aminobutyric acid $_B$ |
| GIRK | G protein gated inwardly rectifying $K^+$ channel |
| Kir | inwardly rectifying $K^+$ channel |
| PKA | protein kinase A |
| PKC | protein kinase C |
| PKG | protein kinase G |
| SK | small-conductance $Ca^{2+}$-activated $K^+$ channel |

## Introduction

Ion channel regulation by receptors for hormones, transmitters and other external stimuli can alter excitability, internal $Ca^{2+}$ concentration, and the level of release of hormones or transmitters. Such regulation allows the activities of a cell to be controlled by the external environment and by other cells, as well as by the cell's own activity, volume, and metabolic state.

Many, but not all, receptors for hormones, transmitters and external sensory stimuli are coupled to G proteins [1–4]. Regulation of ion channels by G protein coupled receptors may be mediated by direct interaction between ion channels and G-protein subunits. Alternatively, channel regulation by G protein coupled receptors may involve the binding of $Ca^{2+}$ or cyclic nucleotides to channels. Both G protein coupled receptors and receptor guanylyl cyclases may also regulate channel activities via protein kinases and phosphatases. Recent studies of receptor-regulated ion channels, from 1996 and late 1995, are selected for this review to provide a glimpse of the range of possible cell regulation.

## $K^+$ channels

### Inwardly rectifying $K^+$ channels

Direct protein–protein interactions between the G-protein βγ subunit and G protein gated inwardly rectifying $K^+$ channels (GIRKs 1–4 in the inwardly rectifying $K^+$ channel [Kir] 3.0 subfamily) [5,6•] are likely to be responsible for the generation of $I_{KACh}$ [7•,8], the current elicited by the parasympathetic transmitter acetylcholine to slow the heart rate [2,3]. Similar mechanisms for GIRK activation may account for some of the effects of inhibitory transmitters in the central nervous system [1,9–13] (Table 1). *In vivo*, G protein gated $K^+$ channels may be heteromultimers; the atrial channels are composed of GIRK1 and GIRK4 subunits [14], whereas GIRK1–GIRK2 multerimeric channels are present in the cortex, hippocampus and cerebellum [15]. In dopaminergic neurons in the midbrain, GIRK2 is the only known GIRK subunit found, and hence may form homomultimeric channels [15,16].

Suppression, or reduction in channel activity, of G protein gated $K^+$ channels and other inwardly rectifying $K^+$ channels may be mediated by substance P and other transmitter receptors that are coupled to the G protein $G_{q/11}$ [11,17,18]. This suppression appears to involve protein kinase C (PKC), and could be potentiated by okadaic acid, a phosphatase inhibitor [17,18] (Table 1). G protein coupled receptors also regulate ATP-sensitive $K^+$ channels ($I_{KATP}$), which are inhibited by cytoplasmic ATP. These channels control insulin release, vascular tone, renal $K^+$ flow, and membrane potential under ischaemic stress [2,3,19–21] (Table 1). The ATP-sensitive $K^+$ channels contain pore-forming subunits of the Kir 6.0 subfamily and other subunits of the ATP-binding cassette (ABC) superfamily; members of the latter family appear to be sensitive to both ATP and the sulfonylurea drugs used to treat diabetes [22].

### Voltage-gated $K^+$ channels

Rapidly inactivating $K^+$ channels such as the *Drosophila Shaker* $K^+$ channel produce transient outward $K^+$ current ($I_A$) upon depolarization of membranes. The $I_A$ current is enhanced by the activation of muscarinic receptors in neostriatal neurons [23] and by activation of the γ-aminobutyric acid $_B$ ($GABA_B$) receptor or the cannabinoid receptor in hippocampal neurons [24,25], as a result of a shift in the voltage-dependence curve of $I_A$ gating. This effect of inhibitory transmitters may be accounted for by

**Table 1**

**Regulation of channels by receptors and second messengers*.**

| Regulated channels | Receptors | Second messenger | References |
|---|---|---|---|
| Potassium channels | | | |
| Kir3.0 (GIRK) | m2AChR, adenosine R | Gβγ activation | [5,6•,7•,8] |
| Kir | m1AChR, subP R | PLC, PKC | [11,17,18] |
| Kir6.0 (K-ATP) | $A_2$ adenosine R | PKA | [19] |
| Kv (A channels) | AChR, cannabinoid R | Reduced PKA | [23–25] |
| M channels | m1AChR, subP R | $Ca^{2+}$? | [26,27] |
| SK | βAR, mGluR | AC, $Ca^{2+}$ | [1,29] |
| BK | AChR, βAR, ANP R | PKG, $Ca^{2+}$ | [30–32,33•,34] |
| cGMP-gated $K^+$ channel | Scallop rhodopsin | cGMP | [35,36] |
| Cation channels | | | |
| cGMP-gated | Rhodopsin | PDE, cGMP | [5] |
| Hyperpolarization-activated | Adenosine R, βAR | cAMP activation? | [9,37] |
| Chloride channels | | | |
| Volume-regulated | P2ATPR, α1AR | PKC | [38,39] |
| Inwardly rectifying | $A_1$ adenosine R | G-protein activation | [40] |
| Sodium channels | | | |
| Amiloride-sensitive | ? | G proteins, C1 | [41] |
| Voltage-gated | AChR, D1 dopamine R | PKC | [42,43•] |
| Calcium channels | | | |
| Voltage-gated | m4AChR, βAR | Gβγ activation | [50–52] |
| Voltage-gated | m1AChR | 'Diffusible' | [46–49] |
| Voltage-insensitive | Antigen R (B cell) | cGMP, PKG | [54•] |
| Internal $Ca^{2+}$ store | Antigen R (mast cell) | Sphingosine-1-P | [55–57] |
| Internal $Ca^{2+}$ store | Taste receptors | $IP_3$ | [58,59] |

*α1 AR, α1 adrenoceptor; βAR, β adrenoceptor; AC, adenylate cyclase; AChR, acetylcholine receptor; $IP_3$, inositol 1,4,5-trisphosphate; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; P2ATRR, $P_2$ ATP receptor; PDE, phosphodiesterase; PLC, phospholipase C; R, receptor; sphingosine-1-P, sphingosine-1-phosphate; subP R, substance P receptor.

a decrease in cAMP concentration and the consequent reduction in protein kinase A (PKA) activity [25] (Table 1).

The M current ($I_M$) is a noninactivating $K^+$ current that is activated at membrane potentials below the threshold for firing an action potential. Suppression of the M current by muscarinic acetylcholine receptors and other $G_{q/11}$-coupled receptors increases neuronal excitability. The M-type $K^+$ channels may be regulated by phosphorylation and by a direct inhibitory effect of cytoplasmic $Ca^{2+}$ [26,27] (Table 1). Similar $Ca^{2+}$-mediated muscarinic modulation of the rat *ether-a-go-go* $K^+$ channel has been reported [28], raising the possibility that some of the M-channel subunits resemble the rat *ether-a-go-go* protein.

### Small-conductance $Ca^{2+}$-activated $K^+$ channels

In principal neurons of the hippocampus and the cortex, inhibition of small-conductance $Ca^{2+}$-activated $K^+$ channel (SK) activities by β-adrenergic receptors increases excitability and results in repetitive firing of action potentials upon prolonged depolarization [1]. From the expressed sequence tag database, potential SK sequences have been retrieved and SKs have been found to resemble voltage-gated $K^+$ channel sequences in design [29]. The SKs are sensitive to $Ca^{2+}$ but not to voltage; unlike the S4 segment of voltage-gated $K^+$ channels which probably functions as part of the voltage sensor, the S4 segment of these SKs does not contain multiple basic residues at every third position [29] (Table 1).

### Large-conductance $Ca^{2+}$-activated $K^+$ channels

The large-conductance $Ca^{2+}$-activated $K^+$ channels (BKs or $K_{Ca}$) are sensitive to both $Ca^{2+}$ and voltage, and are often regulated by G protein coupled receptors. For example, muscarinic receptors and β-adrenergic receptors exert antagonistic effects on BKs of airway smooth muscle [30].

The BKs are also modulated by receptor guanylyl cyclases, such as the receptor for atrial natriuretic peptide (ANP) that regulates blood pressure [31,32]. Activation of ANP receptors elevates cGMP levels and hence protein kinase G (PKG) activity, leading to activation of phosphatase 2A and subsequent activation of the BKs [31]. Remarkably similar processes (i.e. activation via PKG and phosphatase 2A) appear to mediate BK activation by the secreted peptide products of the Alzheimer's β-amyloid precursor protein (β-APP), which can protect neurons under stress [33•,34]. These peptides are generated by presumably proper cleavage of β-APP in its extracellular domain (in contrast to the cleavage in the transmembrane segment of β-APP that occurs when the amyloidogenic Aβ peptides are generated) and are released from central neurons in an

activity-dependent manner [33•] (Table 1). It remains to be determined whether there are receptors for the secreted peptide products of β-APP. If such receptors exist and turn out to belong to the family of receptor guanylyl cyclases, this could account for the similar actions of ANP and the secreted peptide products of β-APP.

### cGMP-gated $K^+$ channels

Unlike rhabdomeric photoreceptors from invertebrates such as *Drosophila*, ciliary photoreceptors from invertebrates such as scallop resemble vertebrate photoreceptors in their use of cGMP to regulate ion channels. Rhodopsin activation in vertebrate photoreceptors leads to reduction of intracellular cGMP levels and closure of cGMP-gated cation channels which normally allow $Na^+$ and $Ca^{2+}$ to go through them [4]. In contrast, light apparently activates cGMP-gated $K^+$ channels in scallop ciliary photoreceptors [35] (Table 1). Despite these differences in phototransduction mechanisms, both processes result in hyperpolarization of the photoreceptor membrane potential. It remains to be determined whether the cGMP-gated $K^+$ channels in scallop ciliary photoreceptors resemble the mammalian cGMP-gated $K^+$ channel [36], which is apparently an evolutionary intermediate between voltage-gated $K^+$ channels and cGMP-gated cation channels.

## Hyperpolarization-activated cation channels

Endogenous adenosine not only activates inwardly rectifying $K^+$ channels but also inhibits the activation of hyperpolarization-activated cation channels, and thereby exerts tonic inhibitory effects on mesopontine cholinergic neurons involved in electroencephalographic (EEG) arousal [9]. Thus, neuronal control of EEG arousal may be affected by alterations of adenosine levels resulting from prior wakefulness or brain hyperthermia. These observations also offer an explanation for the ability of adenosine receptor blockers, such as caffeine and theophyline, to affect arousal [9]. In contrast, norepinephrine, which is released from ascending fibers from the brainstem and involved in the regulation of neuronal activities in the brain during arousal and attention, activates the current $I_h$ by activating the hyperpolarization-activated cation channels in hippocampal pyramidal neurons [37]. This activation can be mimicked by adding cAMP but is insensitive to PKA inhibition, indicating that the hyperpolarization-activated channels give rise to $I_h$ which may be activated directly by cAMP [37] (Table 1). It is not known whether channels giving rise to $I_h$ bear any resemblance to voltage-gated ion channels and cyclic nucleotide gated cation channels.

## $Cl^-$ channels

### Volume-regulated $Cl^-$ channels

Cell volume regulation involves adaptive changes in solute efflux through $K^+$ and $Cl^-$ channels. In rat hepatoma cells, cell swelling increases ATP release, apparently by ATP efflux through anion channels. The released ATP functions as an autocrine factor and activates $P_2$ receptors (a subtype of ATP receptors). This leads to $Cl^-$ channel opening, thereby allowing the cell to decrease its volume [38].

Basal activities of volume-sensitive $Cl^-$ channels appear to account for the basal $Cl^-$ current in rabbit atrial myocytes. Activation of α1 receptors by norepinephrine causes inhibition of these volume-sensitive $Cl^-$ channels in a PKC-dependent manner, as well as inhibition of at least three different $K^+$ channels and stimulation of $Ca^{2+}$ influx [39] (Table 1). The increased $Ca^{2+}$ entry, coupled with a decrease in $K^+$ channel activity and an increase in membrane resistance, may allow α-adrenoceptor stimulation to increase the action potential duration and the force of cardiac contraction. The same alterations in channel activities may also account for the elevated risk of arrhythmia due to stimulation of α-adrenoceptors under stressful conditions.

### Inwardly rectifying $Cl^-$ channels

In hippocampal neurons, membrane-delimited, presumably direct, action of G proteins on inwardly rectifying $Cl^-$ channels increases the channel open probability. This regulation of $Cl^-$ channels may account for the inhibitory effect of the $A_1$ adenosine receptor [40] (Table 1).

## $Na^+$ channels

### Amiloride-sensitive $Na^+$ channels

Epithelial transport of $Na^+$ involves $Na^+$ influx through amiloride-sensitive $Na^+$ channels in the apical membrane of epithelial cells and extrusion of $Na^+$ via the $Na^+K^+$-ATPase in the basolateral membranes. The $Na^+$ influx is controlled via so-called homocellular regulation in order to match the $Na^+$ extrusion rate, so as to maintain cell volume and cytosolic $Na^+$ concentration. It appears that cell volume modulates apical $Na^+$ channels via cytosolic $Cl^-$ and the G proteins $G_{i1}$ or $G_{i2}$, whereas cytosolic $Na^+$ exerts feedback channel regulation via $G_o$ [41] (Table 1). Receptors that might be involved in these regulatory processes have not been identified.

### Voltage-gated $Na^+$ channels

Regulation of neuronal $Na^+$ channels represents part of the modulatory effects of acetylcholine and dopamine in the brain. Voltage-gated $Na^+$ channels in hippocampal neurons may be subjected to modulation by muscarinic receptors via PKC, probably as a result of PKC-mediated phosphorylation of the $Na^+$ channel α subunit [42]. In prefrontal cortex output neurons, activation of D1 receptors by dopamine enhances a slowly inactivating $Na^+$ current and attenuates a slowly inactivating, dendrotoxin-sensitive $K^+$ current in the soma, and it appears to also attenuate high-threshold $Ca^{2+}$ spikes evoked from apical dendrites [43•] (Table 1).

The modulatory effects of dopamine on these ion channels may sharpen the effects of synaptic inputs

from distant association cortical areas. These effects may also enhance the local circuitry concerned with retaining or using previously acquired information to guide a forthcoming response [43•]. Indeed, the working memory for such delayed responses depends critically on D1 receptor activities [44]. Moreover, the impaired neural response of schizophrenic patients to a cognitive task can be enhanced by the administration of apomorphine, a dopamine agonist [45].

## $Ca^{2+}$ channels

### Voltage-gated $Ca^{2+}$ channels

Voltage-gated $Ca^{2+}$ channels constitute a major class of ion channels that are modulated by transmitter receptors. For example, modulation of calcium channels in the nerve terminal regulates $Ca^{2+}$ influx and transmitter release, and β-adrenergic regulation of cardiac $Ca^{2+}$ channels represents one aspect of sympathetic control of the heart [46–49].

There are two ways to inhibit neuronal $Ca^{2+}$ channels, one of which is voltage-dependent and membrane-delimited and the other of which is voltage-independent and involves diffusible second messengers [46]. Different G proteins may mediate these two effects [47,48], and PKC appears to exhibit different effects on these two inhibitory processes [47,49]. The voltage-dependent and membrane-delimited pathway of $Ca^{2+}$ channel inhibition appears to be mediated by direct effects of the G-protein βγ subunits [50,51]. This inhibition is abolished by coexpression of the $\beta_3$ and α subunits of the $Ca^{2+}$ channel, suggesting that association of the α and β subunits of the $Ca^{2+}$ channel may interfere with channel interaction with G-protein subunits [52] (Table 1).

Sympathetic stimulation of the β-adrenergic receptors activates the G protein $G_s$, adenylyl cyclase and cAMP-dependent protein kinase, leading to stimulation of cardiac L-type $Ca^{2+}$ channels [53]. Whereas this pathway involves multiple second messengers that are presumably diffusible, isoprenaline causes only local activation of $Ca^{2+}$ channels. This compartmentalization of cAMP is reduced after inhibition of phosphodiesterase activity, suggesting that it arises from colocalization of enzymes involved in the cAMP cascade [53].

### Voltage-insensitive L-type $Ca^{2+}$ channels

$Ca^{2+}$ channel modulation is not restricted to excitable cells. Cross-linking of B cell antigen receptors with anti-Ig antibodies activates a voltage-insensitive form of L-type $Ca^{2+}$ channels. Structural similarity of these channels to voltage-gated $Ca^{2+}$ channels is suggested by the fact that the voltage-insensitive $Ca^{2+}$ channels in B cells are recognized by antibodies against voltage-gated L-type $Ca^{2+}$ channels [54•] (Table 1).

### $Ca^{2+}$ channels for internal $Ca^{2+}$ stores

Whereas ryanodine receptors and inositol 1,4,5-trisphosphate receptors are known to mediate $Ca^{2+}$ release from internal stores, antigen clustering of IgE receptors on rat mast cells mobilizes $Ca^{2+}$ primarily via sphingosine-1-phosphate, rather than via inositol 1,4,5-trisphosphate [55]. Sphingosine-1-phosphate apparently activates a novel intracellular sphingolipid-gated $Ca^{2+}$-release channel [56,57] (Table 1).

Receptor regulation of $Ca^{2+}$ channels involved in $Ca^{2+}$ release from internal stores [58] is also evident for bitter taste receptors and for receptors activated by sweeteners [59,60]. It remains to be determined how this $Ca^{2+}$ regulation is integrated into the mechanisms of taste sensation. Bitter stimuli activate phosphodiesterase and decrease the cAMP concentration, leading to the opening of cAMP-blocked cation channels. In contrast, sweet taste receptor activation stimulates adenylyl cyclase and increases internal cAMP levels, causing the closure of basolateral $K^+$ channels [59] (Table 1). Knockout of a taste cell specific G protein, gustducin, abolishes both bitter and sweet taste [60], thus posing one more puzzle for cell biologists.

## Conclusions

Ion channels control ion flow, cell volume, and electrical potential across the membrane. The activities of ion channels are sensitive to external and internal signals, which are often mediated by receptors for autocrine or paracrine factors and for hormones and transmitters. The combination of electrophysiological and molecular approaches has continued to expand the horizon of our appreciation of receptor regulation of channels in various cell types. As different receptors and channels are localized to different subcellular compartments or microdomains, one challenge for the future will be to examine channel regulation at important, though not easily accessible, locations such as the nerve terminal.

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Papers of particular interest, published within the annual period of review have been highlighted as:

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