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Review Article

"Cardiac Ion Channels: Insights into Mechanisms and Modulation"

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Abstract: Ion channels play crucial roles in cardiac function, regulating the flow of ions across cell membranes in response to various stimuli. These proteins exhibit selective permeability to specific ions such as Na^+, K^+, Ca^{++} and Cl^- and their gating mechanisms can be voltage-dependent, ligand-dependent, or mechano-sensitive. Sodium channels, for example, are essential for cardiac action potentials and are implicated in various heart pathologies. Mutations in these channels can lead to situations like long QT syndrome and Brugada syndrome. Calcium channels are vital for excitation-contraction coupling, and L-type channels are predominant in cardiac myocytes. They regulate calcium influx, which is crucial for myocardial contraction. T-type channels, although less prevalent in hearts, contribute to pacemaker activity and may influence heart rhythm. Potassium channels, including voltage-gated and inward rectifier channels, are crucial for maintaining the resting membrane potential and regulating action potential duration. Dysfunction of potassium channels are associated with arrhythmias and cardiac pathologies like long QT syndrome. Additionally, the Na^+-K^+ pump maintains cellular ion gradients essential for various physiological processes. Understanding the structure and function of these ion channels provides insights into cardiac physiology and pathophysiology, guiding the development of targeted therapies for heart disorders.

Keywords: Voltage gated ion channels, Na^+ channel, K^+ channel, Ca^{2+} channel, Na+/K+ pump.

INTRODUCTION

Ion channels are proteins that, depending on the stimulus, alter their structure to permit or prohibit the passage of particular ions through a membrane. It is claimed that they have selective permeability. Both internal and external stimuli can act to open or close channels. Examples of external stimuli include when a particular molecule binds to a receptor on a channel or when a sensor detects a change in the membrane potential surrounding the channel. Ion channels are essential for contractility and rhythmicity in the heart, among other aspects of cardiac function. As such, drugs targeting heart pathological conditions like angina or atrial fibrillation include ion channels as one of their primary targets. Ion channels can be selective for particular ions, such as Na^+, K^+, Ca^{++} and Cl- specific channels. They can also be specific to a certain charge of ions, either positively or negatively. The pore formed by an ion channel is aqueous, which allows the ion to travel across the membrane rapidly (Purves 2001). The most significant ions that pass through the cell membrane are Na^+, K^+, Ca^{++}, and Cl^-. These ions do so through specialized ion channels that have the ability to open and close; these channels are referred to as gated channels because they can open and close in response to the following: 1. voltage changes in the channels; 2. Ligand activation to the receptors; 3. Specific ions and chemical ligands. Multiple channels may exist in cardiac cells for a single ion. For instance, a variety of potassium channel types are involved in both action potentials and resting membrane potentials. Ion channels open and close to change certain ion conductance, which in turn controls resting potentials and produces action potentials. For instance, sodium channels momentarily open and potassium channels close in a cardiomyocyte in response to an action potential, resulting in depolarization. To maintain a depolarized condition, the sodium channels close and the calcium channels open within a few milliseconds. Membrane repolarization results from the calcium channels becoming inactive and the potassium channels

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becoming open again. This review describes the generation of the normal cardiac ion channel mechanisms. (Table 1)

Table1: Summary of important ion channels in cardiac and vascular smooth muscle cells and its features

CHANNEL		FEATURES
Major	**Class**	
Sodium Channels	Fast Na^+ Channels	In Phase 0, Non Pacemaker Current cardiac systole
	Slow Na^+ Channels	Pacemaker current (I_f) in cardiac nodal tissue
Potassium Channels	Inward rectifier (I_{ir})	In Phase 3, Cardiac Diastole, Negative Potential
	Transient outward (I_{to})	In Phase 1, Non Pacemaker cardiac potential
	Delayed rectifiers (I_{Kr} and I_{Ks})	In Phase 3, repolarization of cardiac action potentials
	ATP-sensitive ($I_{K, ATP}$)	ATP inhibits K_{ATP} Channel; therefore, in vascular cells, adenosine eliminates the ATP inhibition and opens these channels, producing vascular smooth muscle relaxation and vasodilation.
	Acetylcholine activated ($I_{K, ACh}$)	Gi-protein activates by Acetylcholine
	Calcium Activated ($I_{K, Ca}$ or BK_{Ca})	Ca^{++} influx in vascular smooth muscle
Calcium Channels	L-type (I_{Ca-L})	Phase 2 non-pacemaker contraction cause vascular smooth muscle contraction
	T-type (I_{Ca-T})	In early phase 4 pacemaker currents in SA and AV nodal cells

General Properties of Ion Channels

Ion permeation and gating are the two basic characteristics of ion channels. Ion permeation is the term used to describe the flow via an open channel. The basis for classifying ion channels, such as Na^+ K^+, and Ca^{2+} channels, there is selective permeability to particular ions. The second major property of ion channels is their gating mechanism, which allows them to open and close. Ion channels can be further classified based on the gating mechanism such as voltage-dependent, ligand-dependent, and mechano-sensitive. Voltage-gated ion channels respond to changes in membrane potential by changing their conductance. The most common gating mechanism found in ion channels is voltage-dependent gating. Depolarization causes the majority of ion channels to open. When the membrane becomes hyperpolarized, the pacemaker current channel opens. Each channel has a different voltage dependency for activation or opening (Hille 1984).

Sodium Channels

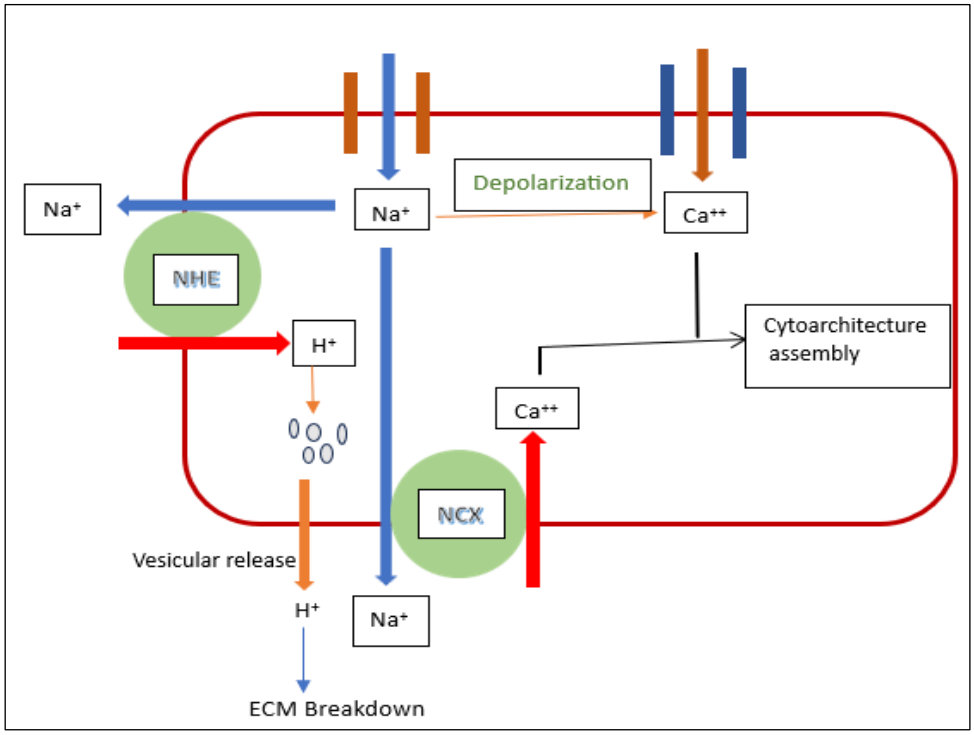

Fig 1: Schematic depictions of the Na+ channel /Calcium channel mechanism

The most basic kind of voltage-gated ion channels are sodium channels (Hodgkin *et al*., 1952). The voltage-gated sodium channel family includes the human cardiac sodium channel, hNaV1.5. A primary α and several secondary β-subunits make up the channel. The α-subunit of hNaV1.5 is adequate to produce sodium current with characteristics similar to the current in native cells when tested in a mammalian expression system. The β1-subunit modifies the gating of the neuronal sodium channel and raises the expression level. It is unknown, if the β1 subunit has a similar function in the cardiac sodium channel. The sodium channel is made up of four homologous domains, DI through DIV, which are organized in a four-fold circular symmetry to produce the channel (Noda *et al*., 1984) (Grant 2009). The segments membrane that bridge the membrane are connected by intra- and extracellular loops that alternate. The pores are formed when the loops known as the 'P' loops, which are located between each domain S5 and S6, curve back into the membrane. Being the transmembrane voltage sensor, each S4 segment contains a positively charged amino acid at every third or fourth position. At high resolution, tiny currents are recordable as a result of these charges moving across the membrane during channel gating. Channel gating has been proposed to be dependent on the transmission of the voltage sensor transition to S-5.

More than 99% of depolarizations involve a single, extremely short opening of a sodium channel (Patlak *et al*., 1985) (Grant *et al*., 1987). On occasion, the channel displays alternate gating modes that include bursts of openings, in which the channel repeatedly opens for hundreds of milliseconds, and isolated, transient openings that follow varying, protracted latencies. The sporadic recovery from the inactivated state is what causes the isolated, temporary openings. The bursts of openings are the result of occasional failure of inactivation (Patlak *et al*., 1985) (YuI *et al*., 1994). Sodium channel mutations that favor these slow gating modes are the basis of a subgroup of the long QT syndromes (Bennett *et al*., 1995). The process of sodium channel inactivation is complex and can take place in milliseconds, seconds, or tens of seconds, depending on how long the preceding depolarization lasted (Richmond *et al*., 1998). The process is quick in response to depolarization that lasts for tens of milliseconds. The region's primary amino acid sequence exhibits high conservation across species and sodium channel subtypes. NMR spectroscopy has resolved the region's tertiary structure (Rohl *et al*., 1999). The putative form of this region is that of a tilting disc that folds into the membrane to occlude the pore. The amino acid triplet isoleucine, phenylalanine, and methionine is essential for sodium channel inactivation; the mutation IFM→QQQ abolishes inactivation (West *et al*., 1992). The triplet's binding receptor site remains unidentified. The carboxyl terminus is also important for sodium channel inactivation. The consensus sites for phosphorylation of the cardiac sodium channel by Ca-calmodulin kinase, protein kinase A (PKA) are present. There is disagreement over the impact of PKA on the INa; some studies report an increase in current, while others report a decrease in current (Ono *et al*., 1989) (Kirstein *et al*., 1996) (Frohnwieser *et al*., 1997). A decrease in INa is the outcome of PKC phosphorylating the channel. Glycerol-3-phosphate dehydrogenase kinase has been shown to modulate the Na+ channel; this was reported recently upon the discovery of an enzyme mutation in a kindred with Brugada syndrome. Enzyme action was linked to a drop in INa, as demonstrated by in vitro expression. The long QT syndrome is caused by errors in inactivation ions that amplify the late component of sodium current. Mutations in the cardiac sodium channel gene SCN5A have been linked to dilated cardiomyopathy, Brugada syndrome, Long QT syndrome (LQTS), and primary cardiac conduction system illness (PCCP). Compared to the peak current, the late component of the current is more susceptible to blocking by class 1 antiarrhythmic medications. Mexiletine and flecainide cause the QT interval to return to normal by lowering the late component of sodium current (Grant 2009) (Wang *et al*., 1997). Patients with LQT3 have benefited from its use, especially those who are young and may present technical challenges for ICD placement. Twenty percent of patients with Brugada syndrome have been shown to have mutations in the sodium channel (Antzelevitch *et al*., 2006). The production of nonfunctional proteins, the protein's inability to bind to the cell membrane, or the channel's quicker inactivation are the reasons why mutations lower the Na^+ current. The patients who have Brugada syndrome due to Na^+ channel mutations exhibit a subset that exhibits prolongation of the H-V interval during ECG testing. The syndrome's T wave inversion and ST segment elevation have a contentious cause. The Na+ channel variation is seen as a conduction deficiency by others, while the syndrome is primarily understood by one group to be a repolarization anomaly (Hong *et al*., 2005) (Zhang *et al*., 2007). The delayed activation of the epicardium is caused by slow conduction from the endocardium to the epicardium. The ST-T wave changes because the transmural repolarization sequence is reversed. Reductions in the Na^+ current are also linked to mutations linked to primary cardiac conduction disease (Schott *et al*., 1999). Sinus node dysfunction, atrial standstill, AV block, and fascicular block are among the clinical syndromes. The same kindred or individual may experience overlap syndromes of LQT3, Brugada syndrome, and PCCD (Grant *et al*., 2002). There is uncertainty regarding the mechanisms by which dilated cardiomyopathy is brought about by Na+ abnormalities (McNair *et al*., 2004). Asynchronous contraction and protracted conduction delay might be involved.

Calcium Channel

The four chambers of a mammalian heart each contain two atria and ventricles. The action potential produced at the right atrium's sino-atrial node controls how much blood is pushed through (Fukuta *et al.*, 2008). Electrical activity in the heart is produced by the accumulation of currents flowing through the different channels (Pullan *et al.*, 2003), (Kurokawa 2007). The cardiac action potential is produced by a number of different ion channel types working in complexes with other proteins in cardiac cells (Grant 2009), (Gururaja *et al.*, 2020), (Singh 2021). A complex network of these channels regulates the cardic myocytes, force of contraction and heart rate. These channels are involved in several heart signaling pathways (Kurokawa 2007). In particular, calcium channels are crucial for the regulation and physiology of cardiac function (Zuccotti *et al*., 2011) (Lam *et al*., 2018) (Hansen 2015) (Shah *et al.*, 2022). In addition to conducting various signaling events like gene transcription, cellular growth processes, bioenergetics, inducing immune response, and tissue remodeling, calcium is a central ion in the electrical activity of the heart, where it connects electrical signals and contraction (Sengupta *et al*., 2021) (Moniri *et al*., 2007) (Ponnalagu *et al*.,2020). The heart's myocardial contraction and pacemaker activity are both impacted by the calcium current (Coetzee 1988). The cardiac action potential's plateau phase is disrupted by subtle alterations in calcium channel activity, which results in an irregular conduction cycle and pathological circumstances including cardiac dysfunction (J Betzenhauser *et al*., 2015). Therefore, the finding and characterization of several of these cardiac calcium channels has resulted from cardiac arrhythmia disorders (Lam *et al.*, 2018) (Hansen 2015) (Shah *et al.*, 2022). To deliver calcium into the cell is the main job of the calcium channels in the sarcolemma of cardiac myocytes (Bers *et al.*, 1999). Specifically, voltage-gated calcium channels are principally responsible for the transport of calcium ions from the extracellular environment into the cell (Nargeot *et al.*, 1997). When contraction is activated, calcium released from the sarcoplasmic reticulum triggers it, and calcium influx helps maintain a higher positive membrane potential (Bers *et al.*, 1999). "Calcium-induced calcium release" (Endo 1977) is the term for this well-known phenomena. Therefore, modulation of these channels serves as an important pharmacological target, given multiple pathologies are implicated when they present an abnormal function. Here, it is important to understand the structural and functional components of calcium channels in the heart. As a result, the excitation–contraction coupling process in cardiac myocytes can proceed without interruption (Nargeot *et al.*, 1997).

Types of Calcium Channels in the Cardiac Tissues

Based on their voltage activation level (high or low), pharmacologic sensitivity, and rate of activation, six kinds of calcium channels have been identified thus far. According to (Kushner *et al.*, 2019), these classes are called T, L, N, P, Q, and R kinds. The majority of calcium channels in the nervous system are N, P, Q, and R kinds. This review will mostly concentrate on the L- and T-type calcium channels due to their expression in cardiomyocytes. The two different types of calcium channels found in the heart are L and T-type, and they are both crucial for controlling cardiac function (Kurokawa 2007). These two varieties are referred as L and T-based on how they react to voltage. Both L-type and T-type voltage-gated calcium channels are "long-lasting" and require a significant depolarization to activate, but T-type channels are "transient" and do not have this property (Kushner *et al.*, 2019). A comprehensive anatomical and functional distinctions, in addition to the changes in time and spatial expression, between these two groups, has enabled the identification of their role in cardiovascular diseases.

L-type calcium channel

Long opening, high voltage-gated calcium channels are known as L-type channels. They manifest in the heart during both developmental and adult stages (Kushner *et al.*, 2019). Since an influx of calcium occurs through them during membrane depolarization, they are crucial and the primary source of excitation–contraction coupling (Nargeot *et al.*, 1997). They are found not only in cardiac tissue but also in skeletal muscle and all excitable cells (Striessnig *et al.*, 2015). The L-type channels are composed of four subunits (P Morrow *et al.*, 2015). They consist of three accessory subunits, beta (β), delta (δ), and gamma (γ), as well as a pore-forming subunit, alpha (α). The α1 subunit forms the pore and central transmembrane machinery, while the β subunit is located on the cytoplasmic side of the complex and interacts with the intracellular domains of the α1 subunit. According to Wu *et al.*, these subunits control gating characteristics, current dynamics, and membrane trafficking. The channel is organized into four domains that are repeated. Six transmembrane segments, S1–S6, make up each of these domains (Singh 2021). The pore domain is made up of the repetitions' S5 and S6 segments. For activation or inactivation states, the voltage sensor is formed by the S1 through S4 segments on each domain. Membrane depolarization causes these channels to open (Nargeot *et al.*, 1997). Extracellular loops with the numbers L5 or L6 have the potential to break up the pore-forming domain (Wu *et al.*, 2015). Structural variability is produced by this as well as variations in the S5 and S6 segment conformations. A selectivity filter is formed by the carbonyl oxygen atoms of the two preceding residues within each repeat, augmented by four glutamate residues on side chains, facilitating specificity. The activity of L-type calcium channels is intimately linked to rapid contraction in cardiac cells, precipitated by transient depolarization events (Nargeot *et al.*, 1997). A series of intracellular events ensure from this, one of which is the activation of the type 2 ryanodine receptor (Marks 2000), which causes a

contraction to occur gradually and persistently (Wu *et al.*, 2015). When it comes to cardiac cells as opposed to aortic cells, the calcium current in these channels inactivates more quickly (Nargeot *et al.*, 1997).

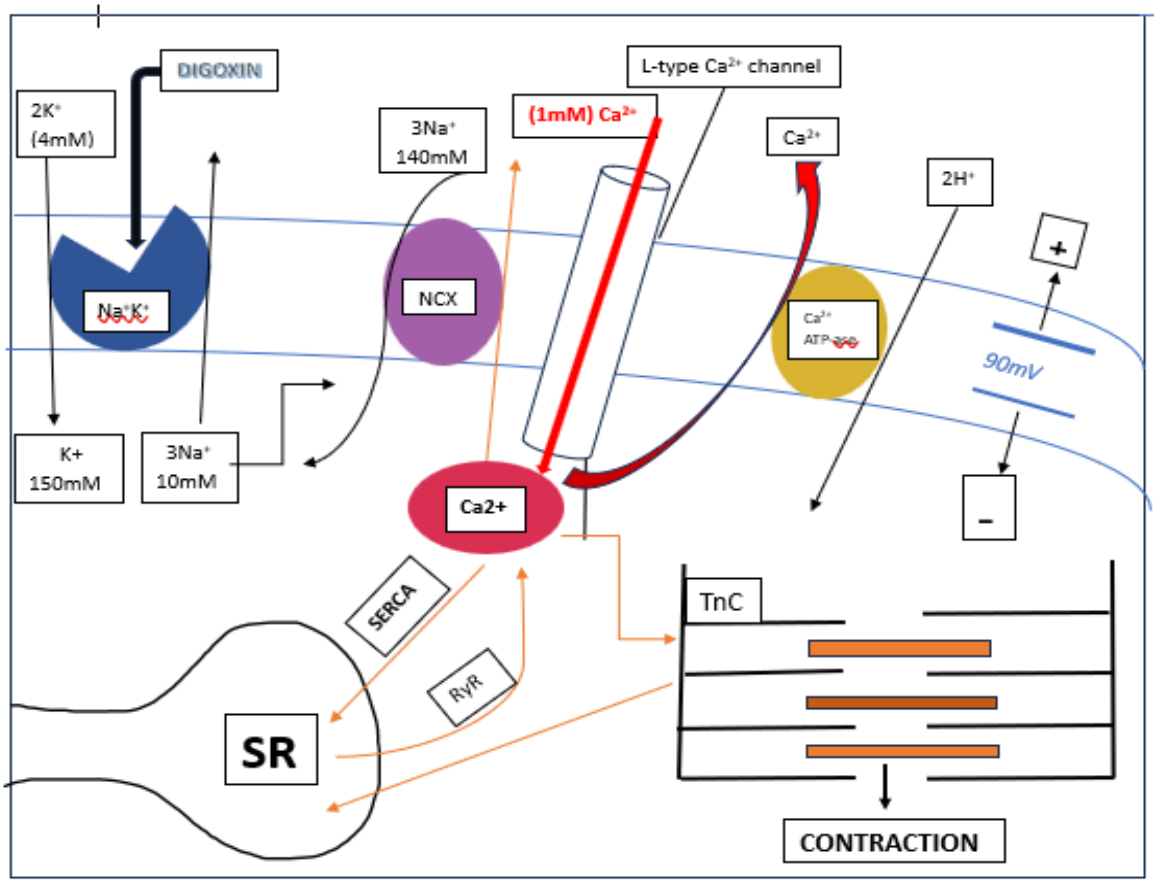

Fig 2: Schematic representation of the calcium channel mechanism

T-type channels

T-type channels are more ephemeral than their L-type counterparts, opening to low-voltage depolarizations. Although their expression decreases with developmental stages, they are functionally expressed in embryonic hearts (Ono *et al.*, 2010). T-type channels are mostly expressed in atrial or sinusoidal cardiac cells rather than ventricular myocytes in the adult heart. The channels exhibit quick inactivation kinetics and activate at a higher negative potential (Weiss *et al.*, 2019). T-type calcium channel structure includes accessory subunits and four homologous domains (P Morrow *et al.*, 2015). According to (Talavera *et al.*, 2006), the intracellular region contains the N and C termini along with three linkers connecting the domains. S1 to S6, the six transmembrane helices that make up the four homologous domains, are described by (P Morrow *et al.*, 2015).Intracellular loops connect these domains; more precisely, they do so between the S1 section of the subsequent domain and the S6 component of the preceding domain (Weiss *et al.*, 2019). The connecting segments of S5 and S6 constitute the pore-forming area, much like the L-type calcium channels. Aspartate or glutamate is one of the four important acidic residues in this area (Weiss *et al.*, 2019). The four domains combine to form a tetrameric structure, which is bordered by the S5–S6 linkers, also referred as p-loops (Talavera *et al.*, 2006). T-type calcium channel selectivity is determined by the configuration of these residues (Weiss *et al.*, 2019). More precisely, two glutamates in domains i, II and two aspartates in domains III and IV combine to form the selectivity filter (Talavera *et al.*, 2006). This is not the same as the four glutamate residues in the selective region of L-type calcium channels (P Morrow *et al.*, 2015). The S4 segment is made up of a positively charged arginine or lysine residue that functions as the voltage sensor (Weiss *et al.*, 2019), much like voltage-gated ion channels (Singh 2021).

T-type calcium channels are found in developing hearts, but their function decreases as the heart grows (Ono *et al.*, 2010). When the heart reaches adulthood, ventricular myocytes' T-type channels are essentially invisible. The majority of them are found in the heart's conduction system (Nargeot *et al.*, 1997). As a result, they depolarize the adult heart's sinoatrial nodal

cells and perform the function of a pacemaker (Ono *et al.*, 2010). Since these channels contribute to pacemaker activity, their abnormal function might cause bradycardia (Hansen 2015). Notably, research has demonstrated that the presence of these channels causes pathological conditions and dysregulation of the excitation–contraction coupling, resulting in aberrant electrical activity in the heart, atria and ventricular myocytes, where L-type calcium channels predominate (Ono *et al*., 2010). It has been demonstrated that adult myocytes with erroneously present T-type channels develop hypertrophied myocytes (Cribbs 2010). This is mostly thought to be caused by T-type channels' involvement in the remodelling of the heart. Moreover, the heart becomes more fibrotic as a result of diastolic dysfunction brought on by the blockage of these channels, which impairs relaxation (Hansen 2015).

Potassium channels

There are three main types of cardiac K+ channels: background K+ currents (TASK-1, TWIK-1/2), inward rectifier channels (IK1, IKAch, and IKATP), and voltage-gated channels (Ito, IKur, IKr, and IKs). The regional variations in the action potential configuration in the atria, ventricles, and across the myocardial wall (endocardium, myocardium and epicardium) are explained by variations in the expression level of these channels. The rationale for the alteration in action potential configuration in response to variations in heart rate is the highly controlled nature of K+ channels. Multiple β-subunits and the primary α-subunit make up voltage-gated K+ channels. The complementary proteins KV-channel associated protein (KChAP) and KV channel interacting protein (KChIP) are also part of the channel functional units. The HERG channel (gene KCNH2), KvLQT1 (gene KCNQ1), and KVN.x (n=1 to 4) are the three main subfamilies of α-subunits. They play a crucial role in the heart's outward current generation. The conserved amino-terminal domains of members of the KVN.x subfamily allow them to coassemble to create hetero-multimers. However, homotetramers are formed by members of the KvLQT1 and HERG subfamilies. Table 1 summarises the several types of K+ channels that are formed by the coamination of α-subunits and their function in generating the action potential. The majority of β-subunits have been sequenced and cloned. They are active oxio-reductases. When the α-subunits are produced in heterogonous systems, they can produce voltage-dependent K+ current. Nevertheless, in order to replicate the K+ currents observed in native cells, the accessory subunits are necessary. KChAP (KCHAP) and KChIP (KCNIP2) have the potential to modify channel kinetics and boost channel activity independently of transcription. One of the four domains of voltage-gated Na+ and Ca2+ channels shares structural similarities with voltage-gated K+ channels. The necessary amino acid sequence for K+ selectivity is glycine-tyrosine-glycine, or GYG.

A K+ current (Ito1) and a Ca2+-activated chloride current (Ito2) make up the transient outward current. Slow and rapid components, Ito,f, and Itos, make up the former. While Ito,f, and Itos are expressed in the ventricle, Ito, f is the primary subtype expressed in the human atrium. The right ventricle, epicardium, and septum are cardiac areas with relatively brief action potentials and greater Ito expression levels. Ito has a quicker activation time constant (<10 ms) than other voltage-gated K+ channels. There is variability and a strong voltage dependence in the inactivation rate. Through PKA-dependent phosphorylation, α-adrenergic stimulation decreases Ito in human myocytes. Angiotensin II and chronic α-adrenergic stimulation both lower channel expression. Different species have different effects when it comes to the duration of the action potential; in rodents, for example, a reduction in Ito results in a longer action potential. In big animals, a decrease in Ito causes the plateau to move towards greater positive potentials, activating the delayed rectifier and accelerating repolarization. A decrease in Ito is linked to an action potential prolongation in a mouse model of hypothyroidism. Human heart failure similarly results in a decrease in current, but this reduction is linked to an extension of the action potential duration. Since Ito determines the plateau's level, modulators that reduce Ito cause the plateau to move into the positive potential range. As a result, ICa and Ca2+ have less electrochemical driving force. The outward currents that are responsible for controlling repolarization are being gradually activated by the delayed rectifier K+ currents IKur, IKr, and IKs. These channels contribute outward current throughout phase 3 repolarization because their deactivation happens slowly enough. The significantly shorter atrial action potential duration is caused by IKur, which is strongly expressed in atrial myocytes. IKr expression varies; it is highest in the ventricular and left atrial endocardium. All cell types express IKs, while midmyocardial myocytes express less of it. The action potential duration of these cells is the longest across the cardiac wall. The most investigated are MinK and MinK-Related Peptide-1 (MiRP-1). Single-membrane spanning peptides with extracellular amino termini are MiRP-1 and MinK. The β-subunits do not conduct, but they control the activity of the α-subunit in response to medications, sympathetic stimulation, and gating. IKr is regulated by β-adrenergic stimulation, which also increases c-AMP and activates protein kinase A. When an agent binds to the channel's cyclic nucleotide binding domain, the former impact is inhibitory while the latter is stimulatory. Inhibitory α-adrenergic stimulation occurs. PKA-dependent phosphorylation of IKs is increased by β-adrenergic activation. PKA, protein phosphatase1, and the adaptor protein yotaio form a complex that is involved in this activity (Marx *et al.*, 2002). LQT1's action potential is prolonged by ion channel alterations that impair the complex's functionality. In LQT1, β-adrenergic blockers have a significant role as treatment choices by indirectly

regulating this complex. In both atrial and ventricular cells, the resting membrane potential is determined by the inward rectifier channel current Ik1. The ventricle has substantially higher levels of channel expression, which shields the ventricular cell from pacemaker action. During phases 0, 1, and 2 of the action potential, the outward current is constrained by the substantial inward rectification of the Ik1. This provides energy efficiency in the action potential production process and restricts the outward current during the action potential's positive phase. Ik1 contributes significantly to phase 3 repolarization because the blockade of the outward current by intracellular Mg+ and the polyamines is eased during repolarization. One of the G protein-coupled inward rectifying potassium channels is the acetylcholine-activated K+ channel. The channel is not as well expressed in the ventricle as it is in the AV, SA, and atria nodes. The action potential is shortened and the membrane potential is hyperpolarized when IKAch is activated. Pacemaker cell depolarization in phase 4 is retarded. The channel architecture resembles that of IK1. Acetylcholine binds to the M2 muscarinic receptor, activating the G protein Gi and causing the subunits Giα and Gβγ to be released. The channel is activated by the dissociated Gβγ subunit, which binds to it. The release of Gβγ and channel activation both follow adenosine's binding to the P1 receptor. Methylxanthines, like theophylline, counteract the effects of adenosine by blocking the P1 receptor. Coexpression of the sulfonylurea receptor and the inward rectifier K+ channel Kir6.x results in channels with characteristics resembling those of the native IKATP. Arrhythmia resulting from improper repolarization are primarily caused by mutations in the genes encoding cardiac K+ channels (Splawski *et al.*, 2000). Most cases of autosomal dominant LQTS (Romano-Ward syndrome) are caused by mutations in the genes encoding KvLQT1 (KCNH2) and HERG (KCNQ1).

Sodium–potassium pump

The Na+ K+ pump is an electrogenic transmembrane ATPase that is located on the cytosolic side of the outer plasma membrane of cells. It was initially identified in 1957 (Skou, 1957) (Pivovarov *et al.*, 2019). For each ATP that is used, the Na+ K+ ATPase pumps three Na+ out of the cell and two K+ into the cell. The lipid bilayer that makes up the plasma membrane is structured asymmetrically and contains proteins, phospholipids, glycolipids, sphingolipids, and cholesterol (Kopec *et al.*, 2014) (Geering 2008). The Na+K+-ATPase pump aids in preserving membrane potential and osmotic balance in cells. Potassium and sodium flow in the opposite direction of concentration gradients. The gradient between a higher amount of potassium intracellularly and a higher concentration of sodium extracellularly is maintained by the Na+ K+-ATPase pump. The persistent concentration gradient has a continuous function in maintaining the resting membrane potential of the cell, controlling the volume of ions in the cell, and facilitating cell signal transmission. It is essential for physiological processes in many organs (Pivovarov *et al.*, 2019). It is essential for numerous physiological functions, including sperm motility, the generation of the neural action potential, and the preservation of waste product filtration in the kidneys' nephrons (Clausen *et al.*, 2017). In addition, the physiological effects of blocking Na+-K+ ATPase are beneficial and the focus of numerous pharmacological uses. Na, K-ATPase is an essential scaffolding protein that interacts with phosphoinositide 3-kinase (PI3K) and protein kinase C (PKC), are the two signaling proteins (Mohammadi *et al.*, 2001).

Cellular Level

The Na+ K+ ATPase is structurally made up of an auxiliary beta subunit and a catalytic alpha subunit (Mercer *et al.*, 1993). One component of the FXYD protein family, which is unique to certain tissues, is present in some Na-K ATPases (Bibert *et al.*, 2011). The transmembrane region of the alpha subunit, known as MA1-M10, is made up of ten helices. Ion binding sites, namely three binding sites that bind to Na+ in the E1 state and two binding sites that bind to K+ in the E2 state, are contained inside these 10 helices (Kanai *et al.*, 2013) (Laursen *et al.*, 2015) (Morth *et al.*, 2007) (Shimoda *et al.*, 2009). The Na-K ATPase has three sites in its structure. In the E1 and E2 states, sites one and two overlap. But site three is only in the E1 state and lies between the transmembrane helices of M5, M6, and M8, which bind to Na+ and catalyse H+ transport (Poulsen *et al.*, 2010) (Ratheal *et al.*, 2010) based on the quantities of Na+, K+, and H+ (Mitchell *et al.*, 2014). Previous research suggests that ion binding pocket protonation may be the cause of the pump's E2 state selectivity for K+ (Yu *et al.*, 2010).

Function

Gradients of sodium and potassium are involved in the physiologic processes of different organ systems (Clausen *et al.*, 2017). Na and K-ATPase are highly expressed in the kidneys; in the distal convoluted tubule, up to 50 million pumps can be expressed per cell. The kidneys need this sodium gradient in order to filter waste materials from the blood, reabsorb glucose and amino acids, control blood electrolyte levels, and maintain pH (El Mernissi *et al.*, 1991). Although sperm cells also use Na, K-ATPase, they do so in a distinct isoform that is required to maintain male fertility. In order to control membrane potential and ions, which is essential for sperm motility and acrosome function after entry into the egg, sperm require Na and K ATPase (Jimenez *et al.*, 2011). Moreover, the brain needs NA^+, K^+ ATPase activity. In order for neurons to produce action potentials, postsynaptic sodium flux must be reversed by the Na, K-ATPase. This restores the potassium and sodium gradients. The sodium gradient is necessary for astrocytes to maintain neurotransmitter reuptake, and this gradient is maintained by the Na, K ATPase pump. About two-thirds of the energy that is

used for protein synthesis and molecular synthesis is absorbed by Na, K ATPases in the grey matter, which means that Na, K ATPases in the grey matter use a large amount of energy (Attwell *et al.*, 2001).

CONCLUSION

Ion channels play pivotal roles in cardiac physiology, regulating ion flow crucial for action potentials and muscle contraction. Dysfunctions in these channels contribute to various cardiac pathologies, understanding the importance of their structure and function for targeted therapeutic interventions in heart disorders.

REFERENCES

- Purves, D., Augustine, G. J., Fitzpatrick, D., Katz, L. C., LaMantia, A. S., McNamara, J. O., & Williams, S. M. (2001). The Molecular Structure of Ion Channels. *Neuroscience; Sinauer Associates: Sunderland, MA, USA*.
- Hille, B. (1984). Ionic channels of excitable membranes. *Sinauer Asso*.
- Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of physiology*, *117*(4), 500.
- Noda, M., Shimizu, S., Tanabe, T., Takai, T., Kayano, T., Ikeda, T., ... & Numa, S. (1984). Primary structure of Electrophorus electricus sodium channel deduced from cDNA sequence. *Nature*, *312*(5990), 121-127.
- Grant, A. O. (2009). Cardiac ion channels. *Circulation: Arrhythmia and Electrophysiology*, *2*(2), 185-194.
- Herbert, E., & Chahine, M. (2006). Clinical aspects and physiopathology of Brugada syndrome: review of current concepts. *Canadian journal of physiology and pharmacology*, *84*(8-9), 795-802.
- Patlak, J. B., & Ortiz, M. A. U. R. I. C. I. O. (1985). Slow currents through single sodium channels of the adult rat heart. *The Journal of general physiology*, *86*(1), 89-104.
- Grant, A. O., & Starmer, C. F. (1987). Mechanisms of closure of cardiac sodium channels in rabbit ventricular myocytes: single-channel analysis. *Circulation research*, *60*(6), 897-913.
- YuI, Z., Starmer, C. F., Starobin, J., & Grant, A. O. (1994). Late Na channels in cardiac cells: the physiological role of background Na channels. *Biophysical journal*, *67*(1), 153-160.
- Bennett, P. B., Yazawa, K., Makita, N., & George Jr, A. L. (1995). Molecular mechanism for an inherited cardiac arrhythmia. *Nature*, *376*(6542), 683-685.
- Richmond, J. E., Featherstone, D. E., Hartmann, H. A., & Ruben, P. C. (1998). Slow inactivation in human cardiac sodium channels. *Biophysical journal*, *74*(6), 2945-2952.
- Rohl, C. A., Boeckman, F. A., Baker, C., Scheuer, T., Catterall, W. A., & Klevit, R. E. (1999). Solution structure of the sodium channel inactivation gate. *Biochemistry*, *38*(3), 855-861.
- West, J. W., Patton, D. E., Scheuer, T., Wang, Y., Goldin, A. L., & Catterall, W. A. (1992). A cluster of hydrophobic amino acid residues required for fast Na (+)-channel inactivation. *Proceedings of the National Academy of Sciences*, *89*(22), 10910-10914.
- Ono, Katsushige., Kiyosue, Tatsuto., & Arita, Makoto. (1989). Isoproterenol, DBcAMP, and forskolin inhibit cardiac sodium current. *American Journal of Physiology-Cell Physiology*, *256*(6), C1131-C1137.
- Kirstein, M., Kochsiek, K., Langenfeld, H., & Eickhorn, R. (1996). Dose-dependent alteration of rat cardiac sodium current by isoproterenol: results from direct measurements on multicellular preparations. *Pflügers Archiv*, *431*, 395-401.
- Frohnwieser, B., Chen, L. Q., Schreibmayer, W., & Kallen, R. G. (1997). Modulation of the human cardiac sodium channel alpha-subunit by cAMP-dependent protein kinase and the responsible sequence domain. *The Journal of physiology*, *498*(2), 309-318.
- Wang, D. W., Yazawa, K., Makita, N., George, A. L., & Bennett, P. B. (1997). Pharmacological targeting of long QT mutant sodium channels. *The Journal of clinical investigation*, *99*(7), 1714-1720.
- Antzelevitch, C., & Fish, J. M. (2006). Therapy for the Brugada syndrome. *Basis and Treatment of Cardiac Arrhythmias*, 305-330.
- Hong, K. U. I., Bjerregaard, P., Gussak, I., & Brugada, R. (2005). Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *Journal of cardiovascular electrophysiology*, *16*(4), 394-396.
- Zhang, Z. S., Tranquillo, J., Neplioueva, V., Bursac, N., & Grant, A. O. (2007). Sodium channel kinetic changes that produce Brugada syndrome or progressive cardiac conduction system disease. *American Journal of Physiology-Heart and Circulatory Physiology*, *292*(1), H399-H407.
- Schott, J. J., Alshinawi, C., Kyndt, F., Probst, V., Hoorntje, T. M., Hulsbeek, M., ... & Le Marec, H. (1999). Cardiac conduction defects associate with mutations in SCN5A. *Nature genetics*, *23*(1), 20-21.
- Grant, A. O., Carboni, M. P., Neplioueva, V., Starmer, C. F., Memmi, M., Napolitano, C., & Priori, S. (2002). Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. *The Journal of clinical investigation*, *110*(8), 1201-1209.
- McNair, W. P., Ku, L., Taylor, M. R., Fain, P. R., Dao, D., Wolfel, E., ... & Familial Cardiomyopathy Registry Research Group. (2004). SCN5A mutation

associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. *Circulation*, *110*(15), 2163-2167.

- Fukuta, H., & Little, W. C. (2008). The cardiac cycle and the physiologic basis of left ventricular contraction, ejection, relaxation, and filling. *Heart failure clinics*, *4*(1), 1-11.
- Pullan, A. J., Buist, M. L., Sands, G. B., Cheng, L. K., & Smith, N. P. (2003). Cardiac electrical activity-from heart to body surface and back again. *Journal of electrocardiology*, *36*, 63-67.
- Kurokawa, J. (2007). Compartmentalized regulations of ion channels in the heart. *Biological and Pharmaceutical Bulletin*, *30*(12), 2231-2237.
- Gururaja Rao, S., Patel, N. J., & Singh, H. (2020). Intracellular chloride channels: novel biomarkers in diseases. *Frontiers in physiology*, *11*, 96.
- Singh, H. (2021). Mitochondrial ion channels in cardiac function. *American Journal of Physiology-Cell Physiology*, *321*(5), C812-C825.
- Zuccotti, A., Clementi, S., Reinbothe, T., Torrente, A., Vandael, D. H., & Pirone, A. (2011). Structural and functional differences between L-type calcium channels: crucial issues for future selective targeting. *Trends in pharmacological sciences*, *32*(6), 366-375.
- Lam, A., Karekar, P., Shah, K., Hariharan, G., Fleyshman, M., Kaur, H., ... & Gururaja Rao, S. (2018). Drosophila voltage-gated calcium channel α1-subunits regulate cardiac function in the aging heart. *Scientific Reports*, *8*(1), 6910.
- Hansen, P. B. (2015). Functional importance of T-type voltage-gated calcium channels in the cardiovascular and renal system: news from the world of knockout mice. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *308*(4), R227-R237.
- Shah, K., Seeley, S., Schulz, C., Fisher, J., & Gururaja Rao, S. (2022). Calcium channels in the heart: disease states and drugs. *Cells*, *11*(6), 943.
- Sengupta, S., West, K. O., Sanghvi, S., Laliotis, G., Agosto, L. M., Lynch, K. W., ... & Guerau-de-Arellano, M. (2021). PRMT5 promotes symmetric dimethylation of RNA processing proteins and modulates activated T cell alternative splicing and Ca2+/NFAT signaling. *Immunohorizons*, *5*(10), 884-897.
- Moniri, N. H., & Daaka, Y. (2007). Agonist-stimulated reactive oxygen species formation regulates β2-adrenergic receptor signal transduction. *Biochemical pharmacology*, *74*(1), 64-73.
- Ponnalagu, D., & Singh, H. (2020). Insights into the role of mitochondrial ion channels in inflammatory response. *Frontiers in physiology*, *11*, 258.
- Coetzee, W. A. (1988). Channel-mediated calcium current in the heart. *Cardiovascular drugs and therapy*, *1*, 447-459.
- J Betzenhauser, M., S Pitt, G., & Antzelevitch, C. (2015). Calcium channel mutations in cardiac arrhythmia syndromes. *Current molecular pharmacology*, *8*(2), 133-142.
- Bers, D. M., & Perez-Reyes, E. (1999). Ca channels in cardiac myocytes: structure and function in Ca influx and intracellular Ca release. *Cardiovascular research*, *42*(2), 339-360.
- Nargeot, J., Lory, P., & Richard, S. (1997). Molecular basis of the diversity of calcium channels in cardiovascular tissues. *European heart journal*, *18*(suppl_A), 15-26.
- Endo, M. (1977). Calcium release from the sarcoplasmic reticulum. *Physiological reviews*, *57*(1), 71-108.
- Kushner, J., Ferrer, X., & Marx, S. O. (2019). Roles and Regulation of Voltage-gated Calcium Channels in Arrhythmias. *The Journal of Innovations in Cardiac Rhythm Management*, *10*(10), 3874.
- Striessnig, J., J Ortner, N., & Pinggera, A. (2015). Pharmacology of L-type calcium channels: novel drugs for old targets?. *Current molecular pharmacology*, *8*(2), 110-122.
- P Morrow, J., & O Marx, S. (2015). Novel approaches to examine the regulation of voltage-gated calcium channels in the heart. *Current Molecular Pharmacology*, *8*(1), 61-68.
- Wu, J., Yan, Z., Li, Z., Yan, C., Lu, S., Dong, M., & Yan, N. (2015). Structure of the voltage-gated calcium channel Cav1. 1 complex. *Science*, *350*(6267), aad2395.
- Marks, A. R. (2000). Cardiac intracellular calcium release channels: role in heart failure. *Circulation research*, *87*(1), 8-11.
- Ono, K., & Iijima, T. (2010). Cardiac T-type Ca2+ channels in the heart. *Journal of molecular and cellular cardiology*, *48*(1), 65-70.
- Weiss, N., & Zamponi, G. W. (2019). T-type calcium channels: from molecule to therapeutic opportunities. *The international journal of biochemistry & cell biology*, *108*, 34-39.
- Talavera, K., & Nilius, B. (2006). Biophysics and structure–function relationship of T-type Ca2+ channels. *Cell calcium*, *40*(2), 97-114.
- Cribbs, L. (2010). T-type calcium channel expression and function in the diseased heart. *Channels*, *4*(6), 447-452.
- Marx, S. O., Kurokawa, J., Reiken, S., Motoike, H., D'Armiento, J., Marks, A. R., & Kass, R. S. (2002). Requirement of a macromolecular signaling complex for β adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. *Science*, *295*(5554), 496-499.
- Splawski, I., Shen, J., Timothy, K. W., Lehmann, M. H., Priori, S., Robinson, J. L., ... & Keating, M. T. (2000). Spectrum of mutations in long-QT syndrome genes: KVLQT1, HERG, SCN5A,

KCNE1, and KCNE2. *Circulation*, *102*(10), 1178-1185.

- Skou, J. C. (1957). The influence of some cations on an adenosine triphosphatase from peripheral nerves. *Biochimica et biophysica acta*, *23*, 394-401.
- Pivovarov, A. S., Calahorro, F., & Walker, R. J. (2019). Na+/K+-pump and neurotransmitter membrane receptors. *Invertebrate Neuroscience*, *19*(1), 1.
- Kopec, W., Loubet, B., Poulsen, H., & Khandelia, H. (2014). The Molecular Mechanism of Na+, K+-ATPase Malfunction in Mutations Characteristic for Adrenal Hypertension. *Biophysical Journal*, *106*(2), 582a-583a.
- Geering, K. (2008). Functional roles of Na, K-ATPase subunits. *Current opinion in nephrology and hypertension*, *17*(5), 526-532.
- Clausen, M. V., Hilbers, F., & Poulsen, H. (2017). The structure and function of the Na, K-ATPase isoforms in health and disease. *Frontiers in physiology*, *8*, 257141.
- Mohammadi, K., Kometiani, P., Xie, Z., & Askari, A. (2001). Role of protein kinase C in the signal pathways that link Na+/K+-ATPase to ERK1/2. *Journal of Biological Chemistry*, *276*(45), 42050-42056.
- Mercer, R. W., Biemesderfer, D., Bliss Jr, D. P., Collins, J. H., & Forbush 3rd, B. (1993). Molecular cloning and immunological characterization of the gamma polypeptide, a small protein associated with the Na, K-ATPase. *The Journal of cell biology*, *121*(3), 579-586.
- Bibert, S., Liu, C. C., Figtree, G. A., Garcia, A., Hamilton, E. J., Marassi, F. M., ... & Rasmussen, H. H. (2011). FXYD proteins reverse inhibition of the Na+-K+ pump mediated by glutathionylation of its β1 subunit. *Journal of Biological Chemistry*, *286*(21), 18562-18572.
- Kanai, R., Ogawa, H., Vilsen, B., Cornelius, F., & Toyoshima, C. (2013). Crystal structure of a Na+-bound Na+, K+-ATPase preceding the E1P state. *Nature*, *502*(7470), 201-206.
- Laursen, M., Gregersen, J. L., Yatime, L., Nissen, P., & Fedosova, N. U. (2015). Structures and characterization of digoxin-and bufalin-bound Na+, K+-ATPase compared with the ouabain-bound complex. *Proceedings of the National Academy of Sciences*, *112*(6), 1755-1760.
- Morth, J. P., Pedersen, B. P., Toustrup-Jensen, M. S., Sørensen, T. L. M., Petersen, J., Andersen, J. P., ... & Nissen, P. (2007). Crystal structure of the sodium–potassium pump. *Nature*, *450*(7172), 1043-1049.
- Shinoda, T., Ogawa, H., Cornelius, F., & Toyoshima, C. (2009). Crystal structure of the sodium–potassium pump at 2.4 Å resolution. *Nature*, *459*(7245), 446-450.
- Poulsen, H., Khandelia, H., Morth, J. P., Bublitz, M., Mouritsen, O. G., Egebjerg, J., & Nissen, P. (2010). Neurological disease mutations compromise a C-terminal ion pathway in the Na+/K+-ATPase. *Nature*, *467*(7311), 99-102.
- Ratheal, I. M., Virgin, G. K., Yu, H., Roux, B., Gatto, C., & Artigas, P. (2010). Selectivity of externally facing ion-binding sites in the Na/K pump to alkali metals and organic cations. *Proceedings of the National Academy of Sciences*, *107*(43), 18718-18723.
- Mitchell, T. J., Zugarramurdi, C., Olivera, J. F., Gatto, C., & Artigas, P. (2014). Sodium and proton effects on inward proton transport through Na/K pumps. *Biophysical Journal*, *106*(12), 2555-2565.
- Yu, H., Noskov, S. Y., & Roux, B. (2010). Two mechanisms of ion selectivity in protein binding sites. *Proceedings of the National Academy of Sciences*, *107*(47), 20329-20334.
- El Mernissi, G., Barlet-Bas, C., Khadouri, C., Marsy, S., Cheval, L., & Doucet, A. (1991). Characterization and localization of ouabain-insensitive Na-dependent ATPase activities along the rat nephron. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1064*(2), 205-211.
- Jimenez, T., McDermott, J. P., Sánchez, G., & Blanco, G. (2011). Na, K-ATPase α4 isoform is essential for sperm fertility. *Proceedings of the National Academy of Sciences*, *108*(2), 644-649.
- Attwell, D., & Laughlin, S. B. (2001). An energy budget for signaling in the grey matter of the brain. *Journal of Cerebral Blood Flow & Metabolism*, *21*(10), 1133-1145.

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