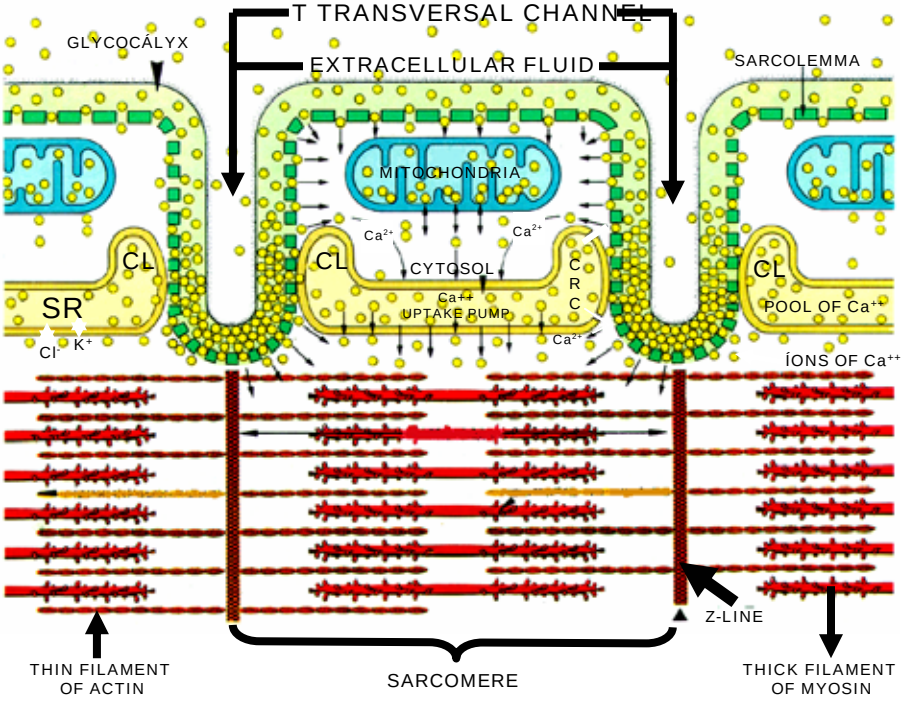
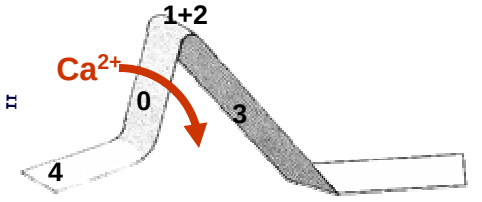

T TRANSVERSAL CHANNEL
EXTRACELLULAR FLUID
GLYCOCALYX
SARCOLEMMA
MITOCHONDRIA
CL
CL
CL
SR
CYTOSOL
C
R
C
Ca++
UPTAKE PUMP
POOL OF Ca++
Cl⁻
K⁺
ÍONS OF Ca++
Z-LINE
THIN FILAMENT
OF ACTIN
SARCOMERE
THICK FILAMENT
OF MYOSIN

CHARACTERISTICS OF SLOW CALCIUM CHANNEL (L CHANNEL $I_{Ca\text{-}L}$)

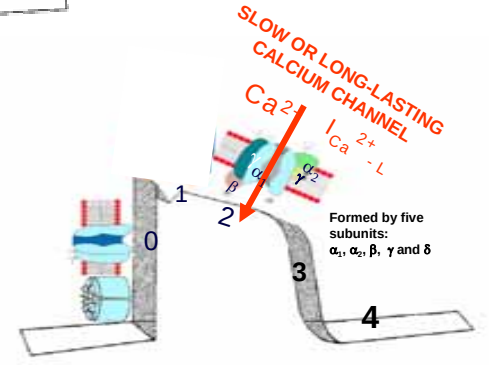
1) **Important in automatic arrhythmias mechanism;**
2) **Responsible for phase 0 of slow fibers;**
3) **Main channel during the plateau or phase 2 in atrial & ventricular muscle cells and in the His-Purkinje system, being in these locations the trigger for Ca^{2+} outflow from the sarcoplasmic reticulum and to induce early after depolarizations (EADs) in phase 3 or bradycardia-dependent;**
4) **Norepinephrine & xantines open the channel increasing Ca^{2+} inflow in phase 2;**
5) **Blocked by dihydropyridinic Ca^{2} antagonists (nifedipine & nitrendipine), as well as benzothiazepine (diltiazem), phenylalkylamine (verapamil), disopyramide, magnesium (Mn), cobalt (Co), cadmium (Cd), zinc (Zn), nickel (Ni) & lanthanum (La).**

I_{CA-L} L-TYPE, SLOW OR LONG-LASTING CHANNELS CHARACTERISTICS



SLOW FIBER

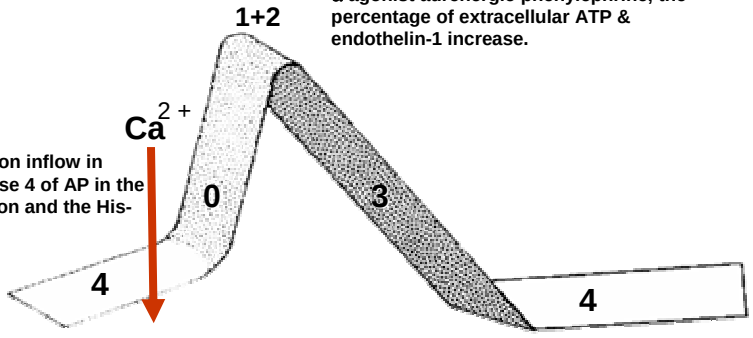
FAST FIBER



FAST T TYPE CHANNELS ($_{ICA\text{-}T}$): TRANSIENT CURRENT OR TINY CONDUCTANCE CHARACTERISTICS

The function of $I_{Ca\text{-}T}$ channels, noradrenaline, α agonist adrenergic phenylephrine, the percentage of extracellular ATP & endothelin-1 increase.

They contribute to ion inflow in the final part of phase 4 of AP in the SA node, the N region and the His-Purkinje system.



Blocked selectively by the Ca^{2+} antagonist mibefradil

Insensitive to dihydropyridine

INTRACELLULAR CALCIUM CHANNELS

1) **PREDOMINANT IN CARDIAC FIBERS OF THE SA NODE AND N REGION OF THE AV NODE (SLOW PHASE 0).**

2) **FORMED BY FIVE SUBUNITS: α_1, α_2, β, γ and δ.**

3) **They contribute to the plateau or phase 2 in atrial and ventricular muscle cells of the His-Purkinje system, being in these locations the trigger for Ca^{2+} outflow from the sarcoplasmic reticulum and to induce early after depolarizations (EADs), in *phase 3* or bradycardia-dependent: relevant role in automatic arrhythmias.**

4) **Phase 0 of slow fibers.**

INTRACELLULAR CALCIUM CHANNELS OF THE SARCOPLASMIC RETICULUM (SR)

I) Ca^{2+} release channel, ryanodine receptor, hyperphosphorilated by protein kinase A (PKA) from the intracellular sarcoplasmic reticulum or CRC "Calcium Release Channel";

II) Ca^{2+} ATPase uptake pump or Ca^{2+} Mg^{2+} ATP_{ase}; (Sarcoplasmic Ca^{2+} ATPase reticulum SERCA));

III) IP3 receptor, Inositol triphosphate or IP_3; inositol 1,4,5 trisphosphate (IP_3) receptor channel.

I) Ca^{2+} RELEASE CHANNEL, RYANODINE RECEPTOR, HYPERPHOSPHORILATED BY PROTEIN KINASE A (PKA) OF INTRACELLULAR SARCOPLASMIC RETICULUM OR CRC "CALCIUM RELEASE CHANNEL"

The SR is an intracellular structure that holds a key role in muscular contraction and relaxation by its capacity of fast release and uptake of myoplasm from the Ca^{2+} ion, by having only in the junctions with the T system of the plasmatic membrane, the so-called Ca^{2+} release channel, CRC (Calcium Release Channel) or ryanodine receptor.

This channel, intracytoplasmatically located in the SR membrane, is very close to the sarcolemmal channels $I_{Ca\text{-}L\ type}$ and like this is voltage and time-dependent. Each $I_{Ca\text{-}L\ type}$ channel controls a group between 4 and 10 ryanodine receptor channels.

I) Ca^{2+} RELEASE CHANNEL, RYANODINE RECEPTOR, HYPERPHOSPHORILATED BY PROTEIN KINASE A (PKA) OF INTRACELLULAR SARCOPLASMIC RETICULUM OR CRC "CALCIUM RELEASE CHANNEL"

Each channel is a large and complex protein of 30 S, formed by four polypeptidic subunits in firm association of M_r ~560.000 with quatrefoil or tetrameric morphology that contours a single hydrophilic, cation-selective pore, with conductance for divalent cations from 100 to 150 pS with 50 mM Ca^{2+} and for monovalent cations of ~750 pS with 250 mM K^+ that is found in the SR membrane and plays its role by releasing the cation of the SR lumen into the cytosol (efflux).

I) Ca^{2+} RELEASE CHANNEL, RYANODINE RECEPTOR, HYPERPHOSPHORILATED BY PROTEIN KINASE A (PKA) OF INTRACELLULAR SARCOPLASMIC RETICULUM OR CRC "CALCIUM RELEASE CHANNEL"

It may be blocked by ryanodine, a toxin derived from an alkaloid plant with nanomolar affinity, and for this reason it is known as ryanodine receptor.

The substances that stimulate this channel improve contractility, and those that block, worsen it. It seems to be the most important channel in heart failure, since a dramatic increase has been observed in its phosphorylation (hyperphosphorylation) in patients with terminal heart failure, what would provide another basis for using β-blockers in this condition.

I) Ca^{2+} RELEASE CHANNEL, RYANODINE RECEPTOR, HYPERPHOSPHORILATED BY PROTEIN KINASE A (PKA) OF INTRACELLULAR SARCOPLASMIC RETICULUM OR CRC "CALCIUM RELEASE CHANNEL"

A recent research points out that patients carriers of familial polymorphic ventricular tachycardia present a missense mutation of the SR in the CRC channel in type 2 ryanodine receptor (RyR2) where three mutations were verified: (P2328S, Q4201R, V4653F).

These mutations were not found in non-affected relatives within the same family and in 100 normal controls.

I) Ca^{2+} RELEASE CHANNEL, RYANODINE RECEPTOR, HYPERPHOSPHORILATED BY PROTEIN KINASE A (PKA) OF INTRACELLULAR SARCOPLASMIC RETICULUM OR CRC "CALCIUM RELEASE CHANNEL"

This entity of early clinical onset and mean mortality rate of 30% up to 30 years old, is characterized by bursts of bidirectional VT and polymorphic VT related to exercise, i.e. catecholamine-dependent with no evidence of structural heart disease.

The gene was mapped in chromosome 1q42-q43.

II) Ca^{2+}-ATPase UPTAKE PUMP or Ca^{2+} Mg^{2+} ATP_{ase}; SARCOPLASMIC Ca^{2+}-(ATPase RETICULUM SERCA)

This pump, with 115kDa of MW and that constitutes a 90% of all the proteins of the SR, introduces the Ca^{2+} within the SR with energetic output. Thus, each 2 mols of hydrolyzed ATP of Ca^{2+} ions are incorporated to the SR.

The greatest regulator of the SERCA pump is the phospholamban, a pentameric protein formed by 5 subunits, each one with MW of 6kDa that inhibits the pump when it is not phosphorylated (phospholamban means phosphate receptor).

II) Ca^{2+}-ATPase UPTAKE PUMP or Ca^{2+} Mg^{2+} ATP_{ase}; SARCOPLASMIC Ca^{2+}-(ATPase RETICULUM SERCA)

When the phospholamban is phosphorylated in response to beta-adrenergic stimulation, the inhibition is blocked and the SERCA pump and the Ca^{2+}- ATPase uptake pump introduce the Ca^{2+} to the SR. The Ca^{2+} that enters into the SR is stocked before a new release in proteins called calsequestrin.

This protein of the SR is located near the T tubules and has a high binding capacity with calcium. Other proteins found are calreticuline, junctin and triadin, which help regulating ryanodine receptor properties.

II) Ca^{2+}-ATPase UPTAKE PUMP or Ca^{2+} Mg^{2+} ATP_{ase}; SARCOPLASMIC Ca^{2+}-(ATPase RETICULUM SERCA)

Recently, a recessive autosomal disease was identified in a family of bedouins that causes a missense mutation that consists of aspartic acid exchange by histidine in calsequestrin 2 (CASQ2), originating a tendency to appearance of catecholaminergic polymorphic ventricular tachycardia with deleterious effect for cation stocking.

II) Ca^{2+}-ATPase UPTAKE PUMP or Ca^{2+} Mg^{2+} ATP_{ase}; SARCOPLASMIC Ca^{2+}-(ATPase RETICULUM SERCA)

The CASQ2 protein is useful for Ca^{2+} stocking in the SR.

Viatchenko-Karpinski et al, by studying CASQ2 with mutations caused by adenoviruses, proved at cellular level, the relationship between the mutation in CASQ2 and the predisposition to adrenergic-induced ventricular arrhythmias, observed in patients carriers of a defect in CASQ2.

II) IP3 RECEPTOR, INOSITOL TRIPHOSPHATE, INOSITOL 1,4,5-TRISPHOSPHATE (IP_3) RECEPTOR CHANNEL

This is another receptor with a high degree of homology with the ryanodine receptor integrated in the membrane of the sarcoplasmic reticulum made up by four equal subunits with six to eight domains each, with a molecular weight of 315,000, with 2749 amino acids, which modulates Ca^{2+} outflow from the sarcoplasmic reticulum into the cytosol, and its trigger and possible modulator is the second cellular messenger, inositol triphosphate or IP_3.

II) IP3 RECEPTOR, INOSITOL TRIPHOSPHATE, INOSITOL 1,4,5-TRISPHOSPHATE (IP_3) RECEPTOR CHANNEL

This is formed from phosphatidyl-inositol-biphosphate that by action of the phospholipase C enzyme is transformed into inositol triphosphate or IP_3.

In turn, this enzyme may be activated by angiotensin II, and α adrenergic stimulation. It is located in Purkinje cells, intercalated disks, conduction system, and in smooth muscles.

$I_{Na^+-Ca^{2+}}$ CHANNEL OR $_{Na^+/Ca^{2+}}$ EXCHANGE CURRENT

1) BY A MECHANISM CALLED ELECTROGENIC, IT EXCHANGES THREE Na^+ MOLECULES BY ONE OF Ca^{2+};

2) IT ACTS IN PHASE 2 OR PLATEAU OF FAST FIBERS;

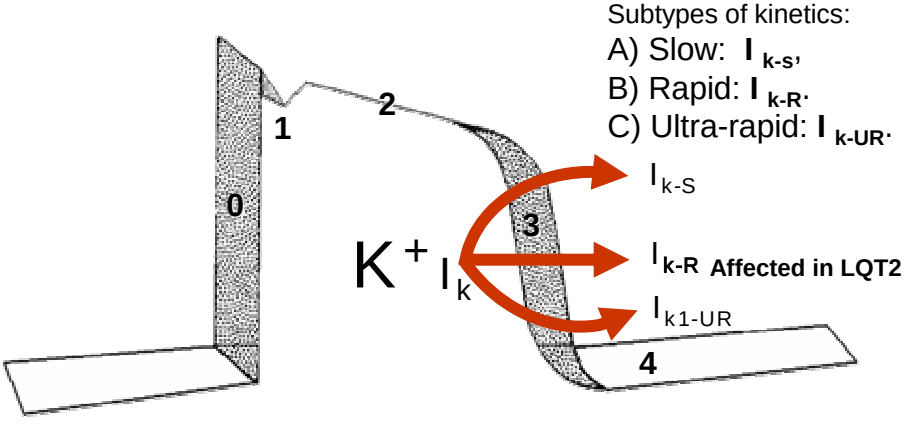
3) IT MAY OPERATE IN BOTH DIRECTIONS: OUTWARDS OR INWARDS;

4) ITS OPERATION DEPENDS ON INTRACELLULAR CONCENTRATION OF Ca^{2+} AND THRESHOLD POTENTIAL;

5) IT ACTIVATES WITH VOLTAGES NEAR THE– 40mV.

VOLTAGE-DEPENDENT, I_K OR DELAYED RECTIFIER CHANNELS

The ion substrate of phase 3 responds to inactivation ($_{ICa\text{-}L}$) and to progressive outflow of K^+ by initial opening of $I_{k\text{-}s}$ and next of $I_{k\text{-}R.}$

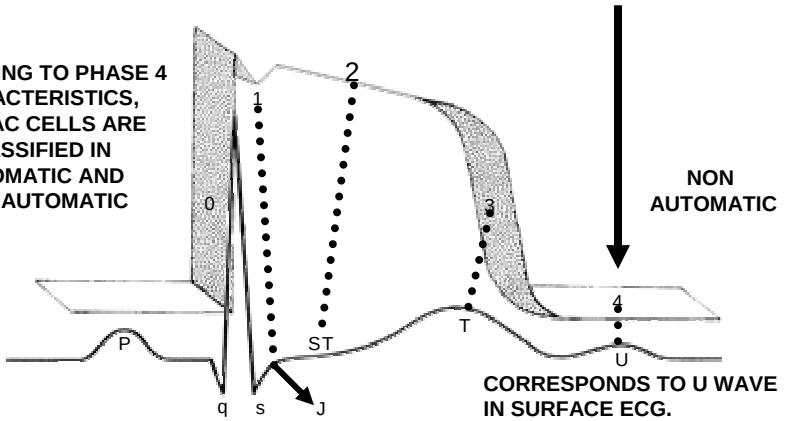


CLASS III ANTIARRHYTHMIC AGENTS (AMIODARONE & SOTALOL) BLOCK K^+ CHANNELS AND CONSEQUENTLY EXTEND TAP. THUS, AMIODARONE BLOCKS THE THREE K^+ OUTFLOW CHANNELS: I_{KS}, I_{KR} & I_{KUR} CAUSING WIDENING, FLATTENING AND NOTCH OF T WAVE.

PHASE 4
CHARACTERISTICS

TYPICAL NON-AUTOMATIC RAPID CELLS: PHASE 4 STABLE. NOT ASCENDING OR HORIZONTAL.
LOCATED IN THE CONTRACTILE CELLS OF ATRIAL AND VENTRICULAR MUSCLES.

ACCORDING TO PHASE 4 CHARACTERISTICS, CARDIAC CELLS ARE CLASSIFIED IN AUTOMATIC AND NON-AUTOMATIC



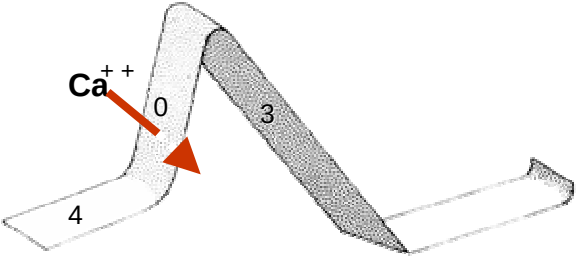
NON AUTOMATIC

CORRESPONDS TO U WAVE IN SURFACE ECG.

PHASE 4

TYPICAL AUTOMATIC FIBER: PHASE 4 UNSTABLE, WITH SPONTANEOUS UPSLOPE, LOCATED IN THE SA NODE, AV NODE (SLOW), AND IN THE HIS-PURKINJE SYSTEM (RAPID)

PHASE 4 AUTOMATIC: ATP YIELDS A HIGH ENERGY LINK (Na^+/ K^+ ATPase PUMP)
CATION EXCHANGE: REINTRODUCES K^+ AND EXPELS Na^+.



PHASE 4 OF THE SA NODE DEPENDS ON THE FOLLOWING CHANNELS:
A) $I_{K(ACH)}$ ACETYLCHOLINE-ACTIVATED INWARD RECTIFYING CURRENT, WHICH PRODUCES HYPERPOLARIZATION AND STIMULATED BRADYCARDIA
B) $I_{ca\text{-}L}$ CHANNEL.
C) I_f, CHANNEL: ACTIVATED BY HYPERPOLARIZATION OR PACEMAKER CHANNEL, INCREASES IMPULSE RATE. IT HAS A PREPONDERANT ROLE IN THE INITIAL PHASE.