$I_{K\text{-}ATP}$, K_{ATP}, rectifier inward K^+ current, activated by muscarinic (M_2) receptors, and stimulated by purinergic I receptors via G protein regulating sign transduction (GTP), Adenosine triphosphate-activated K^+ current or ATP-sensitive K^+ channel.

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The stimulus of this channel occurs when ATP intracellular ratio falls. This occurs in clinics, mainly in myocardial ischemia. The activation of this current causes AP shortening. Pinacidil, cromakalim, and nicorandil also open this channel.

Sulfonylureas, such as glibenclamide, inhibit this channel.

They are K^+ channels (symbolized by KCNJ11), which are expressed in the SA node, AV node, and atrial muscle. When activated, they cause a rectifier inward K^+ current, shorten AP, and cause hyperpolarization and chronotropic and negative dromotropic effects. The activation occurs in the following circumstances:

1) M2 muscarinic receptors stimulation
2) Purinergic type I receptors stimulation via regulators of G protein signaling transduction (GTP)
3) Ischemia causing AP shortening during this state
4) Intracellular AP concentration fall, a fact observed during heart failure with inotropic deficiency
5) Effect of pinacidil, cromakalim, and nicorandil
6) Idiopathic ventricular fibrillation.

Haissaguerre et al **(1;2)** identified a variant of a missense mutation in exon 3 (NC-000012) of KCNJ8 gene, a subunit of the K_{ATP} 2;3 channel. Genomic DNA that sequences K_{ATP} channel genes, showed a missense variant in exon 3 (NC_000012) of the KCNJ8, a subunit of the K_{ATP} channel, providing a predisposition to dramatic changes in repolarization and ventricular vulnerability. From a multicenter cohort of

122 patients (90 men, ages from 37+/-12 years old), carriers of idiopathic ventricular fibrillation (IVF) and early repolarization pattern (ERP) in inferolateral leads, the authors, selected those patients with more than three episodes of ventricular fibrillation(VF), including those with electric storms (≥3 VF in 24 hs). Multiple recurrences of VF occurred in 27% of patients with ERP. Isoproterenol in acute cases and quinidine in chronic patients were effective. The latter is necessary when an ICD is implanted, as it decreases the number of shocks delivered by the device.

The so-called atypical Brugada syndrome is characterized by ST segment and J point elevation in the inferolateral wall. The ERP in the inferolateral wall is not rare in Brugada syndrome **(3).** A high incidence of ERP is observed in inferolateral leads in also in patients with IVF. ECG tracings show QRS-ST joint point elevation ≥0.1 mV in reference to the baseline in inferolateral wall leads and QRS complex notches. Among these patients with history of IVF, ERP prevalence is increased.

Bonakdar et al, **(4)** described a patient carrier of Brugada syndrome, with frequent episodes of syncope. The patient showed alternating ST segment elevation in right precordial leads, and in the high lateral wall. K_{ATP} channels contain a subunit of the Kir6.0 type and sulfonylureas receptors (SUR) **(5).**

By the position they hold within the cell, K_{ATP} channels are identified in three groups:

1) **Sarcolemmal, SarcK_{ATP}.** Made up by 8 protein subunits, with 4 of them being members of the family of the inwardly rectifying potassium channel Kir6.0, and the other 4 being sulfonylureas receptors (SUR1, SUR2A, and SUR2B) **(6).** Kir subunits have 2 transmembrane spans, and they form the pore of the channel. SUR subunits contain 3 additional transmembrane domains, and 2 nucleotide-binding domains in the cytoplasmic surface, with a critical role as sensors of the metabolic state. These SUR subunits are also sensitive to sulfonylureas, MgATP, and some other pharmacological opening channels. Although all sarcK_{ATP} are made up by 8 subunits in a 4:4 ratio, their composition varies with the type of tissue **(7)**.
2) **Mitochondrial (mitoK_{ATP}):** initially identified in 1991 as a single channel, located in the internal portion of the mitochoncrial membrane **(8).** The

molecular structure of the mitoK_{ATP} channels is less known than the one of sarcK_{ATP}. They are composed by Kir6.1 and Kir6.2 subunits, but no SUR1 or SUR2 **(9;10).** They have multiprotein complexes rich in succinate dehydrogenase, with activity similar to the K_{ATP} channel **(11).**

3) **Nuclear K_{ATP} (nucK_{ATP})**. The presence of nuclear KATP was confirmed by the discovery that isolated portions of the nuclear membrane have properties with kinetics and pharmacology similar to the sarcolemmal membrane K_{ATP} **(12).**

Cellular metabolism sensor and genetic expression regulation

Four genes have been identified as being members of the K_{ATP} family. The SUR and kir6.2 genes are located in chromosome 11p15.1; while kir6.1 and SUR2 genes are located in chromosome 12p12.1. The kir6.1 gene encodes the subunit that makes up the K_{ATP} channel pore, with a SUR subunit composed by the sur1 gene, or the selective SUR2 gene (SUR2A and SUR2B) **(13).** Changes in the transcription of these genes, and thus in the production of K_{ATP} channels, are directly related with changes in the milieu metabolism. Thus, hyperglycemia causes kir6.2 decrease at mRNA level. This fact can be reversed by glycemia normalization **(14).** From this, in left ventricular tissue from rats, 1 hour of ischemia followed by 24 to 72 hs of reperfusion, increases kir6.2 transcription in this tissue **(15).**

Crawford et al **(16)** proposed that faced with hypoxia and ischemia, a low level of O_2 decreases the mitochondrial metabolic rate, slowing the Krebs cycle, rendering the organelle incapable of transferring electrons properly, and consequently decreasing the intracellular rate of NAD+NDAH. This lack activates phosphatidylinositol 3-kinase, which is the extracellular signal regulated by kinases. The phenomenon increases the regulation of c-jun transcription, creating a protein that binds to the sur2 promoter. In diabetic patients, K_{ATP} channels, very sensitive to hypoxia, cannot operate properly, leading to a loss of cellular capacity to adapt to an adverse oxidative condition **(17).**

In a condition of hypoxia in the cardiomyocytes, the greatest amount of energy comes from long chain fatty acids, and the equivalents of acetyl-CoA, inducing K_{ATP} channels opening, as long as free fatty acids stabilize the closed shape. This variation has been

experimentally shown in transgenic rats. In the pancreas, unlike cardiomyocytes, the I_{KATP} channels always remain open (**18;19).**

Mitochondrial K_{ATP} and aerobic metabolism regulation

In a condition of hypoxia, the mitochondria starts an overproduction of free radicals **(20).** In this situation, the mitoK_{ATP} channels open and close in an attempt to regulate the internal concentration of Ca^{2+} and the degree of edema of the membrane. This helps to restore the membrane potential properties with H^+ outflow to provide protons for ATP synthesis. Without the contribution of the K^+ channels, there would be a worsening of phosphate depletion of high energy, creating an unfavorable electrochemical transmembrane gradient **(21).** Sarcolemmal and nuclear K_{ATP} channels also contribute to adjustment to hypoxic metabolic stress. With the aim of saving energy, the sarcK_{ATP} channel opens, reducing AP duration as long as the nucK_{ATP} channel regulates the Ca^{2+} concentration within the nucleus, with a protective effect in the expression of genes **(22).**

Cardiovascular K_{ATP} channels and protection from ischemia/ lesion

Cardiac ischemia not always leads to immediate death; frequently, it leads to a slow death of cardiomyocytes by apoptosis, causing a permanent lesion on the cardiac muscle.

A form of ischemia initially described by Keith Reimer in 1986, is characterized by fast and nonlethal tissue compromise, with periods of 3-5 minutes of ischemia, occurring before major ischemic insult. This form of ischemia came to be known as ischemic pre-conditioning (IPC), which is partly dependent on K_{ATP} channel stimulation.

Both sarcK_{ATP} and mitoK_{ATP} channel are required for IPC to achieve its maximal effect. The selective block of mitoK_{ATP} with 5-hydroxydecanoid acid (5-HD) or with MCC-134 (23), completely inhibits the cardioprotection granted by IPC, and affects the genetic expression of the sarcK_{ATP} channel **(24).** Basal protection granted by the sarcK_{ATP} channel, is due to it preventing Ca^{2+} overload, and consequently preventing inotropic depression, saving energy sources **(25).** The absence of sarcK_{ATP} associated to

weakening of the IPC benefit, makes cardiomyocytes to lose their capacity to distribute Ca^{2+}, decreasing sensitivity to the nervous sympathetic signal and predisposing to arrhythmias and sudden cardiac death (**26**). Likewise, sarcK_{ATP} regulates the tone of the vascular smooth muscle; and suppression of the kir6.2 or sur2 genes, leads to artery spasm and death **(27).**

Mutations in the sarcK_{ATP} channel particularly in the SUR2 subunit, lead to dilated cardiomyopathy, especially after ischemia/reperfusion **(28).**

The role of K_{ATP} channel in arrhythmogenesis is still a puzzle. An increase in the conductance of this channel should stabilize the membrane potential during ischemic insult, reducing the extension of the infarction area, and pacemaker ectopic activity. On the contrary, the channel opening and accelerating AP repolarization would enable induction of arrhythmias by reentry **(29).**

References

1) Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008 May 8; 358: 2016-202.
2) Haïssaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquié JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P, Clémenty J. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. J Am Coll Cardiol. 2009 Feb 17; 53: 612-619.
3) Letsas KP, Sacher F, Probst V, Weber R, Knecht S, Kalusche D, Haïssaguerre M, Arentz T. Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome Heart Rhythm. 2008 Dec; 5: 1685-1689.
4) Bonakdar H, Haghjoo M, Sadr-Ameli MA. Brugada Syndrome Manifested by the Typical Electrocardiographic Pattern both in the Right Precordial and the High Lateral Leads. Indian Pacing Electrophysiol J. 2008 Apr 1; 8: 137-140.
5) Stephan D, Winkler M, Kühner P, Russ U, Quast U (2006). "Selectivity of repaglinide and glibenclamide for the pancreatic over the cardiovascular K(ATP) channels.". *Diabetologia* 49 (9): 2039–2048.
6) Inagaki N, Gonoi T, Clement JP4th, Namba N, Inazawa J, Gonzalez G, et al. "Reconstitution of IKATP: An inward rectifier subunit plus the sulfonylurea receptor". *Science.* 1995; 270: 1166–1170.
7) Seino, S, Miki T. "Physiological and pathophysiological roles of ATP-sensitive K+ channels.". *Progress in Biophysics and Molecular Biology* . 2003; 81: 133–176.

8) Zhuo ML, Huang Y, Liu DP, Liang CC. "KATP channel: relation with cell metabolism and role in the cardiovascular system". *The International Journal of Biochemistry and Cell Biology*. 2005; 73: 751–764.
9) Inoue I, Nagase H, Kishi K, Higuti T. "ATP-sensitive K+ channel in the mitochondrial inner membrane.". *Nature*. 1991; 352: 244–247.
10) Lacza Z, Snipes JA, Miller AW, Szabo C, Grover G, Busija DW. Heart mitochondria contain functional ATP-dependent K+ channels. *Journal of Molecular and Cellular Cardiology* . 2003; 35: 1339–1347.
11) Mironova GD, Grigoriev SM, Skarga YY, Negoda AE, Kolomytkin OV. ATP-dependent potassium channel from rat liver mitochondria: Inhibitory analysis, channel clusterization.". *Membrane and Cellular Biology* .1997; 10: 583–591.
12) Quesada, I., Rovira, J. M., Martin, F., Roche, E., Nadal, A., & Soria, B. (2002). "Nuclear KATP channels trigger nuclear Ca(2+) transients that modulate nuclear function.". *Proceedings of the National Academy of Science USA* 99 (14): 9544–9549.
13) Ardehali H, Chen Z, Ko Y, Mejia-Alvarez R, Marban E. Multiprotein complex containing succinate dehydrogenase confers mitochondrial ATP-sensitive K+ channel activity. *Proceedings of the National Academy of Science USA* 101. 2004 Aug; 101: 11880–11885.
14) Aguilar-Bryan L, Clement JP4th, Gonzalez G , Kunjilwar K, Babenko A, Bryan J. Toward understanding the assembly and structure of KATP channels. *Physiological Reviews* 1998 Jan; 78: 227–245.
15) Moritz W, Leech CA, Ferrer J, Habener JF. Regulated expression of adenosine triphosphate-sensitive potassium channel subunits in pancreatic beta-cells. *Endocrinology Journal*. 2001 Jan; 142: 129–138.
16) Akao M, Ohler A, O'Rourke B, Marban E. Mitochondrial ATP-sensitive potassium channels inhibit apoptosis induced by oxidative stress in cardiac cells. *Circulation Research*. 2001Jun 22; 88: 1267–1275.
17) Crawford RM, Jovanović S, Budas GR, Davies AM, Lad H, Wenger RH, Robertson KA, Roy DJ, Ranki HJ, Jovanović A.Chronic mild hypoxia protects heart-derived H9c2 cells against acute hypoxia/reoxygenation by regulating expression of the SUR2A subunit of the ATP-sensitive K+ channel. *Journal of Biological Chemistry*. 2003 Aug 15; 278: 31444–31455.
18) Ren Y, Xu X, Wang X. Altered mRNA expression of ATP-sensitive and inward rectifier potassium channel subunits in streptozotocin-induced diabetic rat heart and aorta. *Journal of Pharmacological Science*. 2003 Dec; 93: 478–483.
19) Koster JC, Marshall BA, Ensor N, Corbett JA, Nichols CG. Targeted overactivity of beta cell K(ATP) channels induces profound neonatal diabetes. *Cell* 2000;100: 645–654.
20) Koster JC, Knopp A, Flagg TP, Markova KP, Sha Q, Enkvetchakul D, Enkvetchakul D, Betsuyaku T, Yamada KA, Nichols CG. (2001). Tolerance for ATP-insensitive K(ATP) channels in transgenic mice. *Circulation Research*. 2001 Nov 23; 89:1022-1029.
21) Zhuo ML, Huang Y, Liu DP, Liang CC. KATP channel: relation with cell metabolism and role in the cardiovascular system. Int J Biochem Cell Biol. 2005 Apr; 37: 751-764.

22) Xu M, Wang Y, Ayub, A., & Ashraf, M. Mitochondrial K(ATP) channel activation reduces anoxic injury by restoring mitochondrial membrane potential. *American Journal of Physiology and Heart Circulation and Physiology* 2001; 281: H1295–H1303.
23) Zhuo ML, HuangY, Liu DP, Liang CC. "KATP channel: relation with cell metabolism and role in the cardiovascular system". *The International Journal of Biochemistry and Cell Biology* .2005; 73: 751–764.
24) Mubagwa K, Flameng W. "Adenosine, adenosine receptors and myocardial protection: An updated overview. *Cardiovascular Research.* 2001; 52: 25–39.
25) Suzuki M, Saito T, Sato T, Tamagawa M, Miki T, Seino S, Nakayama H. Cardioprotective effect of diazoxide is mediated by activation of sarcolemmal but not mitochondrial ATP-sensitive potassium channels in mice. *Circulation.* 2003; 107: 682–685.
26) Gong, B., Miki, T., Seino, S., & Renaud, J. M. (2000). "A K(ATP) channel deficiency affects resting tension, not contractile force, during fatigue in skeletal muscle.". *American Journal of Physiology* and Cell Physiology *279 (5): C1351–C1358.*).
27) Zingman, L. V., Hodgson, D. M., Bast, P. H., Kane, G. C., Perez- Terzic, C., Gumina, R. J., et al. (2002). "Kir6.2 is required for adaptation to stress.". *Proceedings of the National Academy of Science USA* 99 (20): 13278–13283..
28) Chutkow, W. A., Pu, J., Wheeler, M. T., Wada, T., Makielski, J. C., Burant, C. F., et al. (2002). "Episodic coronary artery vasospasm and hypertension develop in the absence of Sur2 K(ATP) channels.". *Journal of Clinical Investigation* 110 (2): 203–208.
29) Bienengraeber, M., Olson, (.T. M., Selivanov, V. A., Kathmann, E. C., O'Cochlain, F., Gao, F., et al. (2004). "ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic KATP channel gating.". *Nature Genetics* 36 (4): 382–387.