Research News

Human congenital long QT syndrome: more than previously thought?

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Mutations in KCNQ1 and KCNE1, the α- and β-subunits of the I_{KS} K^+ channel, produce the cardiac long QT (LQT) syndrome. These subunits are expressed in heart and inner ear, but also in epithelial tissues such as kidney or intestine where their functional roles have remained elusive. Recent work has shown that KCNE1-deficient mice display chronic hypokalemia and hyperaldosteronism. These results have significant implications for human congenital LQT syndromes because hypokalemia increases the risk of ventricular arrhythmia and cardiac sudden death.

The slowly activating I_{KS} K^+ current is found mainly in the heart and inner ear. The molecular correlate of the I_{KS} K^+ channel complex was recently shown to consist of the heteromeric assembly of α- and β-subunits called KCNQ1 (also known as KvLQT1) and KCNE1 (also known as IsK or minK), respectively [1,2] (Fig. 1). Mutations in the genes encoding KCNQ1 and KCNE1 produce the long QT (LQT) syndrome, a human, genetically heterogeneous cardiovascular disease that is characterized by abnormal ventricular repolarization [3–6]. Two clinical forms of inherited LQTs are recognized: (1) the Romano–Ward syndrome, mainly transmitted in an autosomal dominant pattern of inheritance; and (2) the Jervell and Lange–Nielsen (JLN) syndrome, which, in addition to exhibiting cardiac symptoms, is associated with congenital bilateral deafness and is transmitted in an autosomal recessive pattern of inheritance.

KCNQ1 and KCNE1 proteins are not confined to the heart and the inner ear but are also abundantly expressed in many epithelial tissues (i.e. kidney, intestine, lung, thymus or pancreas) where no clear functional role of these proteins has been ascribed as yet.

Altered K^+ balance and hyperaldosteronism in KCNE1-deficient mice

A new development in this field came recently from exciting work by Arrighi *et al.* [7], who used null mutant *Kcne1* mice that lacked the I_{KS} K^+ current but could still express KCNQ1-mediated currents. Although mice have a different action potential configuration and faster heart rates compared with humans, murine knockouts of *Kcne1* or *Kcnq1* might represent an interesting model for the human JLN syndrome. In KCNE1$^{-/-}$ mice, the baseline electrocardiogram (ECG) is normal; however, there is an exacerbated QT adaptation to heart rate, as is also observed in LQT1 patients (those who possess mutations in the KCNQ1 channel α-subunit) [8]. In their recent work, Arrighi *et al.* showed that on a normal K^+ diet, KCNE1$^{-/-}$ mice display chronic hypovolemia (reduced effective circulating blood volume) and hypokalemia (low plasma K^+ concentration), associated with fecal Na^+ and K^+ wasting and higher plasma concentrations of aldosterone than wild-type mice [7]. A high K^+ diet leads to a fivefold larger increase of plasma aldosterone concentrations in KCNE1$^{-/-}$ mice than in wild-type mice. This hyperaldosteronism is associated with abnormally high plasma renin concentrations; however, KCNE1$^{-/-}$ and wild-type mice have similar blood pressure [7]. Because hypokalemia increases the risk of ventricular arrhythmia, these data have significant implications for the LQT syndrome. Although JLN patients are reported to have normal kalemia [9], an exacerbation of the aldosterone response to stimuli might lead to hypokalemia. In this context, administration of intravenous K^+ in adjunct with magnesium could represent a useful therapy.

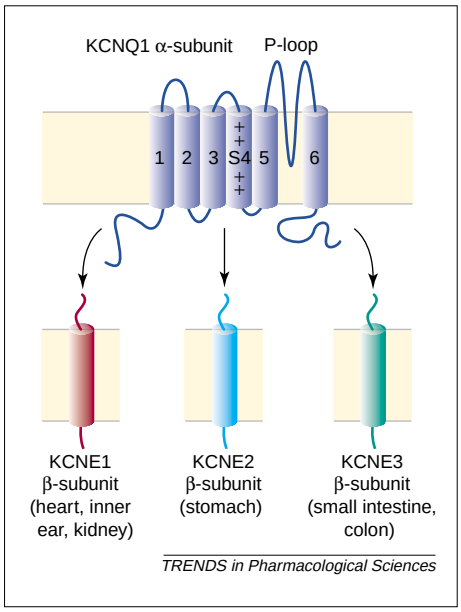

Fig. 1. The KCNQ1 α-subunit belongs to a newly characterized K^+ channel gene family, *Kcnq*, whose products (KCNQ1–5) are typical members of the voltage-gated K^+ channel superfamily with six putative transmembrane segments, including a voltage sensor S4 and a P-loop domain bearing the K^+-selectivity signature [4,6]. The KCNE1 β-subunit has a single putative transmembrane segment and cannot form K^+ channels on its own [17]. It is a typical member of the KCNE family (KCNE1–5) of small β-subunits that modulate the activity of various voltage-gated channels, including KCNQ, K_v and HCN channels [17–20]. The KCNQ1 α-subunit can associate with KCNE1 in heart, inner ear and kidney to form the I_{KS} K^+ channel complex. KCNQ1 can also associate with KCNE2 in stomach and with KCNE3 in small intestine and colon.

Interestingly, it was found that KCNE1 and KCNQ1 mRNAs are coexpressed in mouse adrenal cortex in the zona glomerulosa, the region in which aldosterone is secreted [7]. The combined phenotype of hypokalemia and hyperaldosteronism can arise from a primary epithelial defect and/or from a primary adrenocortical dysfunction.

Hypokalemia and primary epithelial defects

Long-term maintenance of K^+ balance depends on both the colon and the kidney, which adjust the rate of K^+ secretion and absorption to dietary intake. KCNE1 and KCNQ1 proteins were recently found to colocalize in the apical membrane of proximal tubular kidney cells [10] (Fig. 2a). Reduced K^+ secretion in proximal tubules and increased fractional urinary excretion of fluid, Na^+, Cl^- and glucose were found in KCNE1$^{-/-}$ mice, compared with wild-type mice [10]. This is consistent with the volume depletion observed in KCNE1$^{-/-}$ mice [7]. In this context, hypokalemia probably occurs because a fraction of the Na^+ excreted

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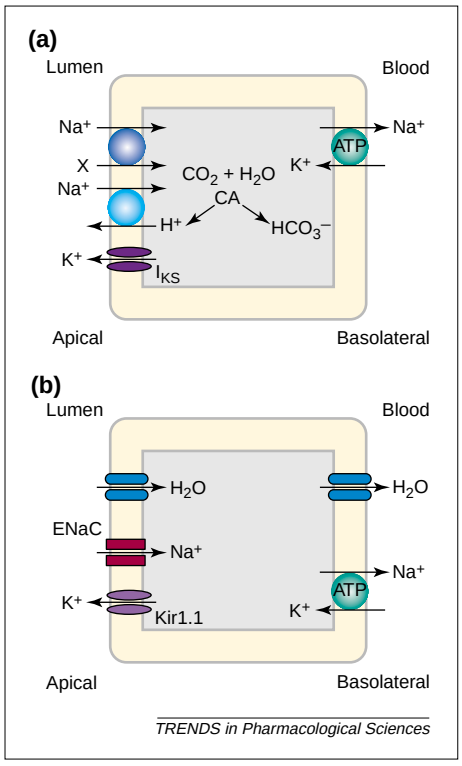

Fig. 2. Transport processes in the proximal tubule (a) and distal convoluted tubule and cortical collecting duct (b) of the kidney. In proximal tubule cells (a), reabsorption of Na^+ is effected by apical Na^+-coupled cotransporters. The Na^+–X cotransport protein indicates the presence of five unique symporters, where X represents either glucose, amino acid, phosphate, Cl^- or lactate. Na^+ entry is also coupled with extrusion of H+ from the cell by the Na^+–H^+ antiporter. Within proximal tubule cells, CO_2 and H_2O combine to form H^+ and HCO_3^- via carbonic anhydrase (CA). Na^+ enters the blood via the basolateral Na^+–K^+-ATPase pump, which provides the electrochemical driving force for apical Na^+ entry. Secretion of K^+ into the lumen probably involves apical IKS K^+ channels. In distal convoluted tubule and cortical duct cells (b), Na^+ reabsorption occurs mainly via apical ENaC Na^+ channels. This produces an osmotic uptake of water through water channels. Secretion of K^+ into the lumen is effected via apical Kir1.1 K^+ channels. K^+ secretion is facilitated by the depolarization produced by apical Na^+ entry. Aldosterone leads to absorption of Na^+ and simultaneous excretion of K^+ in kidney epithelial cells of the distal tubule and cortical collecting ducts by stimulating apical ENaC channel and basolateral Na^+–K^+-ATPase activities. The apical membrane depolarization caused by Na^+ uptake increases the driving force for luminal K^+ efflux. Aldosterone also causes secretion of H^+ in exchange for Na^+.

is reabsorbed in downstream distal tubule segments through the epithelial Na^+ channel ENaC (Fig. 2b), the activity of which is upregulated by hyperaldosteronism. Increased activity of ENaC is associated with enhanced K^+ secretion at the level of the distal tubule segment, leading to reduced plasma K^+ concentrations. Unknown compensatory mechanisms probably limit global renal dysfunction. Although KCNE1 mRNA expression was detected recently in distal convoluted tubules and in cortical collecting ducts [11], the functional significance of this localization needs to be explored. Hypokalemia might also result, in part, from the chronic loss of K^+ in the feces of KCNE1$^{-/-}$ mice. This K^+ wasting would directly result from increased amiloride-sensitive Na^+ reabsorption (probably via ENaC channels) that is observed in the colon of KCNE1$^{-/-}$ mice [7]. The fecal Na^+ wasting does not appear to arise from a defective Na^+ reabsorption via ENaC channels but might involve the other Na^+ entry pathway via the intestinal Na^+–H^+ antiporter, a possibility that remains to be tested. This Na^+ loss also contributes to chronic hypovolemia and hyperaldosteronism.

Hypokalemia and primary hyperaldosteronism

The hypokalemia found in KCNE1$^{-/-}$ mice might also arise from primary hyperaldosteronism. Aldosterone is secreted from the zona glomerulosa of the adrenal cortex, mainly in response to signals arising from the kidney, when a reduction in fluid volume is sensed. In response to Na^+ deprivation, the fall in extracellular fluid and plasma volume causes the juxtaglomerular cells of the kidney to secrete renin into the peripheral circulation. Renin acts on angiotensinogen to form angiotensin I, which is cleaved by angiotensin-converting enzyme to form angiotensin II (Ang II). This potent vasoconstrictor binds to specific Ang II AT_1 receptors in the zona glomerulosa of the adrenal cortex, which then leads to the release of aldosterone from the adrenal cortex. Aldosterone causes absorption of Na^+ and simultaneous excretion of K^+ in kidney epithelial cells of the distal tubule (Fig. 2b) and in cortical collecting ducts of the kidney in addition to in epithelial colonic cells. Aldosterone exerts these effects by: (1) increasing Na^+ uptake via apical ENaC channels by enhancing ENaC channel open probability and channel synthesis [12]; (2) enhancing the basolateral Na^+–K^+-ATPase activity; and (3) stimulating the Krebs cycle in mitochondria to provide energy for basolateral Na^+ extrusion. The apical membrane depolarization caused by Na^+ uptake will increase the driving force for luminal K^+ efflux (Fig. 2b). This explains why increased ENaC channel activity such as that occurring in Liddle's syndrome is associated with hypokalemia [3]. Although aldosterone mainly causes K^+ to be secreted in exchange for Na^+, to a smaller extent, it also causes secretion of H^+ in exchange for Na^+ (Fig. 2a).

The lack of KCNE1 does not appear to affect the basal secretion of aldosterone directly. The results of Arrighi *et al.* [7] suggest that KCNE1 controls aldosterone secretion induced by extracellular K^+. However, it is not yet clear whether the hyperaldosteronism of KCNE1$^{-/-}$ mice fed a normal K^+ diet results from the chronic fecal Na^+ wasting or whether other unknown mechanisms are involved. The main physiological activators of aldosterone secretion are high plasma K^+, Ang II and adrenocorticotropic hormone (ACTH). ACTH acts primarily via cAMP whereas high plasma K^+ and Ang II lead to elevation of free cytoplasmic [Ca^{2+}]. The negative resting membrane potential of glomerulosa cells mainly results from a high K^+ permeability. Recent studies showed that TASK-1, a member of the two-pore domain K^+ channel family, contributes to the generation of this high resting K^+ permeability [13]. Inhibition of the resting K^+ conductance by activated AT_1 receptors depolarizes the glomerulosa cell membrane and opens T-type Ca^{2+} channels [13].

In light of the coexpression of KCNQ1 and KCNE1 in zona glomerulosa cells, Arrighi *et al.* suggest that I_{KS} channels could be implicated in the regulation of aldosterone synthesis and secretion induced by elevation of extracellular K^+ (Fig. 3). Even small elevations of extracellular K^+ concentration can lead to membrane depolarization that is sufficient to open T-type voltage-gated Ca^{2+} channels, which in turn further depolarizes the cell. This profound depolarization should activate voltage-gated K^+ channels, including I_{KS} channels, which will dampen the depolarizing effect of inward currents and limit Ca^{2+} influx and aldosterone secretion (Fig. 3).

The results of Arrighi *et al.* [7] convincingly suggest that I_{KS} channels represent one of the K^+ conductances that limit aldosterone secretion. It should be kept in mind, however, that the glomerulosa cell membrane is endowed with other voltage-gated K^+ conductances in addition to Ca^{2+}-activated K^+ channels and inward-rectifier K^+ channels. It remains to be determined whether these additional K^+ conductances contribute to the regulation of aldosterone secretion or to the maintenance of the polarized resting membrane potential.

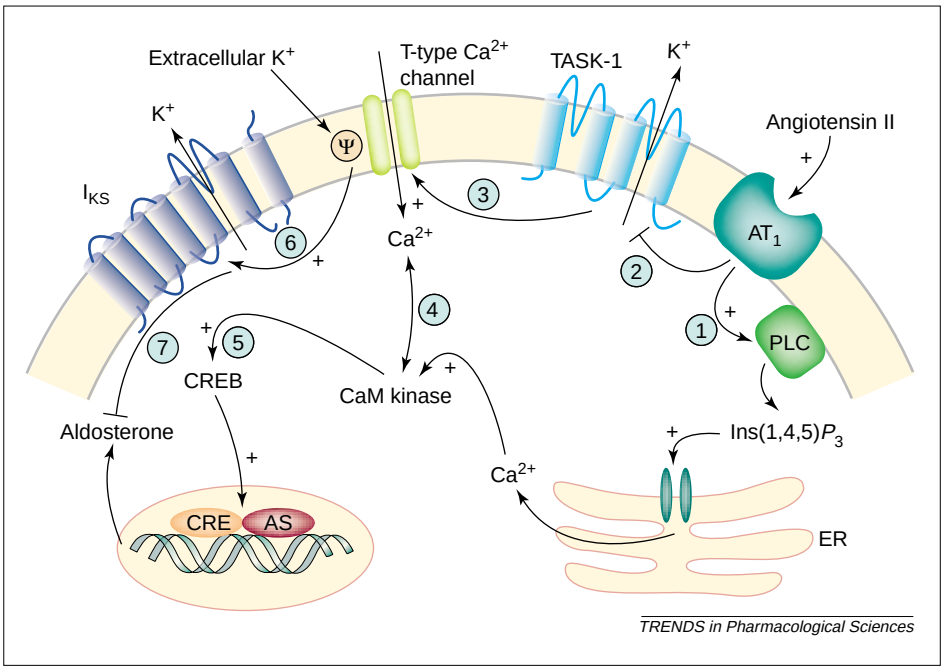

Fig. 3. Hypothetical role of I_{KS} K^+ channels in the control of aldosterone secretion in zona glomerulosa cells of the adrenal cortex. (1) Binding of angiotensin II to angiotensin AT_1 receptors activates phospholipase C (PLC), which generates inositol (1,4,5)-trisphosphate [Ins(1,4,5)P_3] and releases Ca^{2+} from intracellular stores. (2) Inhibition of a resting K^+ conductance (probably encoded by the two-pore domain TASK-1 K^+ channel) by AT_1 receptors depolarizes the glomerulosa cell membrane, which activates T-type voltage-gated Ca^{2+} channels (3) and produces a sustained Ca^{2+} influx. (4) The release of stored Ca^{2+} is thought to activate a calmodulin-dependent protein kinase (CaM kinase), which phosphorylates the T-type Ca^{2+} channels, shifting their voltage dependence to more negative potentials. This leftward shift makes T-type Ca^{2+} channels more likely to open in response to small depolarizing changes in membrane potentials. Thus, even small elevations of extracellular K^+ concentration can lead to membrane depolarization that is sufficient to open T-type voltage-gated Ca^{2+} channels, which in turn further depolarizes the cell. Aldosterone secretion is controlled by the activity of aldosterone synthase (AS). (5) Increases in intracellular Ca^{2+} resulting from extracellular K^+-driven signals and/or AT_1 receptor activation lead to transcriptional activation of the gene encoding aldosterone synthase via a CRE-like cis-element, and production of aldosterone. However, the profound depolarization should activate voltage-gated K^+ channels, including I_{KS} channels (6), which will dampen the depolarizing effect of inward currents and limit Ca^{2+} influx and aldosterone secretion (7). Abbreviations: CREB, cAMP response element-binding protein; ER, endoplasmic reticulum.

Lessons from *Kcne1* and *Kcnq1* knockout mice

The central findings of Arrighi *et al.* [7] suggest that the I_{KS} channel plays a crucial role in K^+ homeostasis and in the regulation of aldosterone and renin secretion. These data have profound pathophysiological implications for human congenital LQT syndromes.

In addition to their direct cardiac impact, KCNE1 or KCNQ1 mutations could affect renal proximal tubule and adrenal cortex functions. By inducing hypokalemia and hyperaldosteronism, these I_{KS} channel defects might increase the risk of torsades de pointes ventricular arrhythmia and cardiac sudden death in affected individuals. Obviously, one must remain cautious in extrapolating data from mice to humans, particularly because species differences in the tissue distribution of these channels are known. For example, KCNE1 is expressed in rodent stomach whereas it is absent from human gastric tissue [14]. Thus, it will be important to identify whether KCNE1 and KCNQ1 proteins are present in human adrenal cortex. Recent work performed in *Kcne1* and *Kcnq1* knockout mice [15,16] suggest that KCNQ1 (possibly associated with KCNE2) might be required for normal acid secretion and, while associated with KCNE1, KCNQ1 could play a crucial role in T-cell homeostasis. Together, these studies provide a basis to explore further the functional anomalies of patients with congenital LQT syndrome.

Acknowledgements

This work is supported by the Israel Science Foundation (grant no. 540/01–1).

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