Human congenital long QT syndrome: more than previously thought?

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Mutations in KCNQ1 and KCNE1, the β-subunits of the IKS 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 IKS K-current is found mainly in the heart and inner ear. The molecular correlate of the IKS K-current in KCNQ1-deficient mice was recently shown to consist of the heteromeric assembly of α- and β-subunits called KCNQ1 and KCNE1 (alkso known as KvLQT1 and KvLQT2, 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 their functional roles have been ascribed by 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 β-subunit 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 LQTS patients (those who possess mutations in the KCNQ1 channel β-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+-rich 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 kalaemia [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.

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
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 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\(^+\) influx. Aldosterone also causes secretion of H\(^+\) in exchange for Na\(^+\).

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 is 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 a MAPK pathway whereas high plasma K\(^+\) and Ang II lead to elevation of free cytoplasmic [Ca\(^{2+}\)]. The negative resting membrane potential of glomerulosa cells is 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.

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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\(_2\)O 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\(^+\) influx.
Lessons from Kcne1 and KCNQ1 knockout mice

The central findings of Arrighi et al. [7] suggest that the IKS 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, KCNQ1 or KCNQ2 mutations could affect renal proximal tubule and adrenal cortex functions. By inducing hypokalemia and hyperaldosteronism, these IKS 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).

References


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