The multifaceted phenotype of the knockout mouse for the KCNE1 potassium channel gene

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Warth, Richard, and Jacques Barhanin. The multifaceted phenotype of the knockout mouse for the KCNE1 potassium channel gene. Am J Physiol Regulatory Integrative Comp Physiol 282: R639–R648, 2002; 10.1152/ajpregu.00649.2001.—Mutations of the KCNE1 gene (IsK, minK) are related to hereditary forms of cardiac arrhythmias, so-called long QT syndromes (LQT). Here we review the phenotype of a mouse model for the recessive form of LQT known as Jervell and Lange-Nielsen syndrome. KCNE1 knockout mice exhibit an enhanced QT-RR adaptability, which is probably part of the pathophysiological mechanism leading to life-threatening tachyarrhythmia in patients. Like patients, knockout mice are deaf and show vestibular symptoms due to an impaired endolymph production. Knockout mice show urinary and fecal salt wasting and volume depletion. The renal phenotype is due to diminished reabsorption of Na⁺/H⁺ and glucose. The mice are hypokalemic and have increased aldosterone levels. Besides volume depletion, aldosterone is elevated via a set-point shift for sensing of extracellular K⁺ in aldosterone-secreting glomerulosa cells, which physiologically express KCNE1. In conclusion, KCNE1 knockout leads to a complex phenotype resulting from direct loss of KCNE1 and compensatory mechanisms. Murine KCNE1 physiology could be helpful for the pathophysiological understanding and perhaps gene-specific treatment of long QT patients.

KvLQT1; long QT syndrome; kidney; heart

POTASSIUM CHANNELS are found in virtually all mammalian cells. They form the most diverse group of ion channels (~80 pore-forming subunit genes) that can be divided into three main structural classes comprising two, four, or six transmembrane segments. All these K⁺ channel subunits have in common a conserved motif called the P domain, which is part of the K⁺-selective filter that provides the specificity to K⁺ transport. In addition to the pore-forming subunits themselves, K⁺ channels comprise in their structure associated modulatory subunits designated as β-subunits. They are usually not essential for the formation of the ionic pore, but they determine the stability of the channel complex in the membrane and modulate biophysical, regulatory, and pharmacological properties (18).

KCNE1, also named IsK or minK, belongs to a family of small transmembrane proteins (KCNE1, -2, -3, and -4 and KCNE1L). Originally KCNE1 was cloned from a rat kidney library and expressed in Xenopus laevis oocytes, leading to a slowly activating K⁺ current (IKs) (70). However, KCNE1 has been regarded as somewhat of an enigma in the ion channel field because it has none of the hallmarks of conventional K⁺ channels, particularly the P domain. Moreover, it was found that the amplitude of KCNE1 currents in oocytes saturates at low levels of cRNA injections (9), and attempts to express KCNE1 currents in numerous eukaryotic cells failed (42). These observations indicated the lack of an essential cofactor in these cells. The explanation of this phenomenon is the coassembly of KCNE1 with a Shaker-type K⁺ channel α-subunit, KCNQ1 (also named KvLQT1), identified by positional cloning in patients with long QT syndrome (6, 17, 61). KCNQ1...
exists as an endogenous X. laevis KCNQ1 in oocytes (61). The assembly with KCNE1 increases the voltage dependence and current amplitude of KCNQ1, slows down activation kinetics, and changes pharmacological properties (Fig. 1, A and B) (10). Mutations in both genes are associated with a hereditary form of cardiac arrhythmia, so-called long QT syndromes (7, 38, 55). Monoallelic mutations in either gene cause the dominant form of the syndrome, called Romano-Ward syndrome (RWS; long QT syndrome type 5), a life-threatening disease characterized by prolonged cardiac repolarization and polymorph ventricular arrhythmias. Biallelic mutations lead to the Jervell and Lange-Nielsen syndrome (JLNS), with a severe long QT phenotype associated with profound bilateral deafness (51, 73). In the case of the RWS, mutations in other ion channel genes have also been described (for review, see Refs. 38, 57). These genes include the Na+ channel gene SCN5A and two K+ channel genes, KCNH2 (HERG) and KCNE2 (MiRP1), the latter encoding a protein similar to KCNE1. In addition, two other gene loci have been described that correspond to a ryanodine receptor (RYR2) on chromosome 1q42 (56) and a yet unknown gene on 4q25 (62).

Besides its assembly with KCNQ1, KCNE1 was also shown to associate with KCNH2 (48) and Cl− channels (4). However, these two types of interactions are less documented than the one with KCNQ1 and still await confirmation. On the other hand, it is clear that in addition to KCNE1, both KCNE2 (71) and KCNE3 (63) can interact with KCNQ1 to form K+ channels with specific biophysical properties (for review, see Ref. 60). The KCNE1/KCNQ1 channel complex is abundant in heart muscle, inner ear, and a variety of epithelial tissues (Fig. 2) (8, 65). The generation of a null mutant mouse for the KCNE1 allows the detailed in vivo exploration of the physiological roles of this specific channel in cardiac as well as noncardiac tissues. In humans the KCNE1 gene is located on chromosome 21q22.1-q22.2 (15) and in mice on chromosome 16 (64.4 cM) (Ref. 37). For construction of the knockout mouse the complete coding sequence (located on exon 2) was deleted and replaced by the neomycin resistance gene (75). In another KCNE1 knockout mouse model, in addition to deletion of the KCNE1 coding sequence, lacZ and neomycin resistance genes were inserted (40).
Moreover, a spontaneous mutation leading to a truncated protein (66 instead of 129 amino acids) has been reported (43). The clinical relevance of KCNE1 mutations in humans is known for heart and inner ear. Here we give an overview on the multitissue phenotype of the KCNE1 knockout mouse, which could have an impact for human pathophysiology and disease.

**KCNE1 KNOCKOUT MICE DISPLAY A MILD CARDIAC PHENOTYPE**

Physiologically, repolarization of heart action potential is dependent on several K⁺ conductances, including KCNE1/KCNQ1. The cardiac KCNE1/KCNQ1 current (Iₖₑ) is activated via depolarization during the action potential and shows slow activation kinetics. In mouse heart, KCNE1 is strongly expressed with some decay during the first weeks after birth (25, 27). With PCR methods, we find KCNE1 abundant in both atrium and ventricle (Fig. 2). β-Galactosidase activity, which was under control of the KCNE1 promoter, indicates a strong and specific expression of KCNE1 in cells of the sinus node and atrioventricular node, in lower right atrial septum, and in the proximal conducting system. In the ventricle, cells belonging to the conducting system are also stained (40).

Does KCNE1 gene disruption affect the heart action potential? In one study microelectrode measurements show no difference in action potential duration between knockout and wild-type mice (13). In electrocardiogram recordings, there is no direct correlate of the QT prolongation observed in JLNS patients: QT interval is very similar in both genotypes under control condition and in the presence of isoproterenol stimulation (25, 40). However, the QT-RR adaptation is significantly exacerbated in KCNE1 knockout mice, leading to a prolonged QT interval during bradycardia (25). A similar increased QT-RR adaptability is described for long QT patients (33, 50). What, then, is the explanation for the shorter QT intervals in knockout mice at high heart rates? One might speculate that KCNQ1 alone, which is still present in KCNE1 knockout mice, could lead to a fast-activating repolarizing K⁺ current at high heart rates. Furthermore, secondary compensatory effects, i.e., via differences in plasma K⁺ or high aldosterone, are possible explanations.

Taken together, the KCNE1 knockout mouse is an interesting model for JLNS, but with clear limitations due to species differences. Concerning the localization of KCNE1 in pacemaker cells and the conducting system, especially in the lower right atrium, it is speculated that KCNE1 might play a role in common reentrant arrhythmias such as atrioventricular nodal reentrant tachycardia and common atrial flutter (40). Further studies are needed to elucidate the underlying mechanisms and a possible role of KCNE1 in more detail.

**KCNE1 GENE KNOCKOUT IS ASSOCIATED WITH DEAFNESS AND SHAKER-WALTZER BEHAVIOR**

Endolympth is an extracellular fluid with a unique composition, a high K⁺ concentration (150 mmol/l) and a low Na⁺ concentration (4 mmol/l). The ionic composition is crucial for signal transduction of sensory hair cells of the cochlear duct and the vestibular labyrinth. Numerous genes are known to cause deafness (http://www.uia.ac.be/dnalab/hhh/). Among these, some genes for membrane transporters and ion channels have been identified that are involved in the complex mechanisms (69, 76) of endolympth secretion and generation of the endocochlear potential: Na⁺-2Cl⁻-K⁺ cotransporter (21, 24, 28), H⁺ ATPase (36), and KCNE1/KCNQ1 K⁺ channels. KCNE1 and KCNQ1 are localized in the luminal membrane of endolympth-producing marginal cells from the stria vascularis and of vestibular dark cells (11, 41, 52, 59, 75) representing the efflux pathway for K⁺. Their regulation by purinergic (47), adrenergic (78), and muscarinic (77) receptors and cAMP (67, 68) and their pharmacology (64) have been described in detail.

Already in the 19th century cases of sudden death combined with deafness were reported (49) probably corresponding to JLNS. Like patients suffering from JLNS, KCNE1 knockout mice are also profoundly and bilaterally deaf and exhibit an obvious vestibular dysfunction, leading to rapid head bobbing and bidirectional circling, which is referred to as Shaker-Waltzer behavior (23, 40, 43, 75).

In the cochlea of the inner ear the position of Reissner’s membrane is dependent on the balance between endolympth production and reabsorption. In KCNE1 knockout mice, Reissner’s membrane collapses postnatally, indicating that K⁺ secretion and concomitant water flux are strongly reduced. This impaired endolympth production leads to cell death of sensory hair cells and, within 6 wk, to degeneration of the majority of the spiral ganglion neurons (75). Interestingly, the cell layers of stria vascularis show slight morphological changes, namely an enlargement of the intercellular space in the intermediate cell layer, which corresponds to fluid waiting to be secreted. The endolympth-producing marginal cells appear to be grossly normal (75). In the vestibular labyrinth the vestibular wall collapses, similar to Reissner’s membrane in the cochlea. Within 6–7 mo after birth, the sensory hair cells of the vestibular system degenerate and disappear. Endolympth-producing vestibular dark cells of KCNE1 knockout mice are larger but do not undergo cell death (52). In Ussing chamber experiments short-circuit current as a measure of secretion is almost completely abolished in KCNE1 knockout mice (75). Interestingly, KCNQ1 immunostaining of the luminal membrane of dark cells disappears in KCNE1 −/− mice, indicating that KCNE1 is essential for KCNQ1 membrane targeting and/or stability of KCNQ1 in the membrane (Fig. 3) (52). It is not presently known if KCNE1 also plays...
such a trafficking role in other organs where it is associated with KCNQ1. More recently, it was shown that KCNQ1 knockout mice present similar inner ear pathology (11, 41).

In conclusion, the heteromultimeric KCNE1/KCNQ1 channel plays a key role for physiological endolymph secretion, which is a prerequisite for signal transduction in cochlea and vestibular system. In addition, KCNE1 is essential for normal KCNQ1 localization and function in the inner ear.

ROLE OF KCNE1 FOR RENAL SALT AND WATER REABSORPTION

In mammalian kidney, KCNE1 is predominantly expressed in proximal tubules. Immunofluorescence experiments reveal a colocalization of KCNE1 and KCNQ1 proteins in the brush-border membrane (22, 66, 74). However, a weaker expression of KCNE1 and KCNQ1 in other nephron segments is not excluded by these experiments.

Is renal function affected by KCNE1 gene knockout? Interestingly, KCNE1 ∓/₋ mice are hypokalemic and exhibit as a sign of dehydration an increased hematocrit, suggesting an impaired renal electrolyte balance and enhanced water loss (Fig. 4) (3, 74). The inulin clearance as a measure of glomerular filtration rate is not changed; however, the fractional excretion of NaCl and fluid is markedly increased. Micropuncture experiments reveal a reduced K⁺ concentration in late proximal and early distal tubular fluid of knockout mice due to a reduced proximal tubular K⁺ efflux through luminal KCNE1 K⁺ channels (74).

Proximal tubules physiologically reabsorb Na⁺ and substrates using Na⁺/H⁺ exchange (NHE3) and Na⁺-coupled glucose and amino acid transport systems. This Na⁺-coupled transport depolarizes the luminal membrane, thereby reducing the driving force for further transport. Thus luminal K⁺ channels are required to repolarize the luminal membrane. In studies on isolated in vitro perfused proximal tubules of KCNE1 ∓/₋ mice, phenylalanine and glucose in the luminal fluid led to an enhanced depolarization of the membrane voltage compared with wild-type mice. The gene knockout could be mimicked by addition of the K⁺ channel inhibitor Ba₂⁺ to the luminal fluid in perfused proximal tubules of wild-type mice (74). This loss of driving force for substrate reabsorption explains the increased fractional glucose excretion of KCNE1 ∓/₋ mice. To exclude additional effects of the knockout on distal nephron segments, amiloride can be used as a pharmacological tool to assess Na⁺ reabsorption via epithelial Na⁺ channels (ENaC). Interestingly, amilo-

Fig. 3. Immunolocalization of KCNE1 and KCNQ1 in the vestibular system. A: KCNE1 staining of a KCNE1 wild-type vestibular crista. The endolymphatic space is located at top right. At the base of each side of the crista, the luminal membrane of dark cells is strongly stained (arrows). Other parts of the crista, sensory and transitional epithelium, are not labeled. B: KCNQ1 staining of a KCNE1 wild-type vestibular crista. As with KCNE1 protein, a strong luminal staining of KCNQ1 (arrows) was detected. C: KCNQ1 staining of a KCNE1 knockout vestibular crista. Compared with wild type in B, the KCNQ1-specific staining is lost. Please note the changes in morphology and the collapse of the endolymphatic space (*). Figure 3 is a kind gift from Marie-Thérèse Nicolas and Danielle Demémes, Monpeiller, France (published with permission).
ride gives rise to a higher Na\(^+\) excretion in knockout mice, which argues against an impaired reabsorption of distal nephron segments.

Taken together, these data indicate an important role of the KCNE1/KCNQ1 complex as a luminal K\(^+\) channel in mouse proximal tubules. This K\(^+\) conductance located in the brush-border membrane grants the driving force for electrogenic Na\(^+\) and substrate reabsorption.

**ALDOSTERONE SECRETION IS REGULATED BY KCNE1-DEPENDENT K\(^+\) CONDUCTANCE**

Under normal diet, KCNE1 \(-/-\) mice exhibit hypokalemia and hypokalemia. Probably, the hypokalemia is mostly due to an increased plasma aldosterone concentration (Fig. 5). Interestingly, plasma renin concentrations under normal diet are similar in both wild-type and knockout mice, indicating that the increase in aldosterone is not due to enhanced renin concentration. In KCNE1 knockout mice high aldosterone stimulates Na\(^+\) reabsorption in distal colon, paralleled by enhanced K\(^+\) secretion and fecal K\(^+\) loss. Also, renal fractional K\(^+\) excretion is enhanced but does not reach significance. Low-Na\(^+\) diet increases and low-K\(^+\) diet reduces aldosterone plasma concentrations in both genotypes in a similar way. In contrast, under high-K\(^+\) diet, aldosterone is approximately fivefold higher in KCNE1 \(-/-\) mice, although plasma K\(^+\) concentration is still lower than in wild-type mice (3). The explanation for this surprising finding is the expression of KCNE1 in aldosterone-producing adrenal glomerulosa cells. Physiologically, aldosterone secretion is activated via two major stimuli: high plasma K\(^+\) concentration and ANG II, both finally leading to the activation of depolarization-activated T-type Ca\(^{2+}\) channels. This Ca\(^{2+}\) influx then in turn activates aldosterone secretion. The K\(^+\) conductance in glomerulosa cells comprises at least two types of K\(^+\) channels. ANG II inhibits one type, namely TASK1 (19), via Ca\(^{2+}\)/calmodulin-dependent protein kinase II and shifts the voltage dependence of the T-type Ca\(^{2+}\) channel to more hyperpolarized values (14). On the other hand, even small increases in plasma K\(^+\) suffice to depolarize the cell, thereby activating Ca\(^{2+}\) influx. This depolarization is thought to activate voltage-dependent K\(^+\) channels, which then limit the Ca\(^{2+}\) influx and aldosterone secretion (45). The impressive effect of high-K\(^+\) diet in KCNE1 \(-/-\) mice, together with the increased aldosterone under normal K\(^+\) diet without a concomitant increase in renin, indicates a crucial role of KCNE1 for repolarization of glomerulosa cells. A portion of the increase in aldosterone under high-K\(^+\) diet is caused via renin. The elevated renin is probably not due to a direct effect of the KCNE1 gene deletion on renin-producing cells because they do not express KCNE1. The mechanism by which renin is increased remains to be elucidated. Taken together, these data suggest a concerted mechanism of action of the increased renin/ANG II concentration and enhanced K\(^+\) sensitivity of glomerulosa cells in KCNE1 \(-/-\) mice.

Further studies are required to investigate the impact of these data on human pathology. Both low plasma K\(^+\) and high aldosterone concentrations are possibly harmful: the occurrence of life-threatening torsades de pointes arrhythmias in patients suffering from long QT syndromes is especially high during hypokalemia (26, 58). On the other hand, aldosterone was shown to have a deleterious effect on the progression of chronic heart failure (54).
KCNE1 IN EXOCRINE PANCREAS

KCNE1 and KCNQ1 are abundant in pancreatic acinar cells (22, 70, 80), leading to a voltage-dependent and slowly activating $\mathbf{K}$ current (39). In wild-type mice, KCNQ1 seems to be mainly located in the basolateral membrane. However, it cannot be excluded that KCNQ1 is present to a weaker extent in luminal and vesicular membranes. Interestingly, in KCNE1/−/− mice, KCNQ1-specific immunofluorescence is less focused on the basolateral membrane and also present in the cytosol, suggesting an impaired membrane targeting of KCNQ1 (79). In addition, the pancreatic secretory granules are irregularly distributed in KCNE1/−/− mice: some acini are completely packed with granules, whereas other acini are almost without any secretory granules. Unfortunately, the pathophysiological mechanisms underlying this phenomenon are not understood.

The biophysical properties of the KCNE1/KCNQ1 $\mathbf{K}$ current in pancreatic acini resemble very much the cardiac KCNE1/KCNQ1 channel complex (6, 61) and the voltage-dependent current observed in adrenal glomerulosa cells (6, 45). This component of whole cell $\mathbf{K}$ current is strongly augmented in the washout phase after cholinergic stimulation when the intracellular $\mathbf{Ca}^{2+}$ activity and the $\mathbf{Ca}^{2+}$-activated $\mathbf{Cl}^{-}$ conductance are already decreased. In pancreatic acinar cells of KCNE1/−/− mice, this current is almost completely abolished, indicating, together with the histological findings, a functional role of KCNE1 in the KCNQ1 channel complex in rodent pancreas (79). Further studies are needed to elucidate the localization and physiological role of KCNE1 during electrolyte and enzyme secretion.

INTESTINAL ION TRANSPORT IS ALTERED IN KCNE1/−/− MICE

In metabolic cage experiments KCNE1/−/− mice lose an impressive amount of $\mathbf{Na}^{+}$ and $\mathbf{K}^{+}$ with feces compared with wild-type mice (3). The loss of $\mathbf{K}^{+}$ might be explained by an increased secretion in distal colon due to stimulated aldosterone secretion in knockout mice. In fact, we observe in KCNE1/−/− mice threefold increased amiloride-sensitive $\mathbf{Na}^{+}$ reabsorption in Ussing chamber experiments of distal colon. Intriguingly, this observation cannot explain the increased $\mathbf{Na}^{+}$ loss via feces in metabolic cages, but one would expect the opposite, namely a reduced loss of $\mathbf{Na}^{+}$. One might speculate that similar to $\mathbf{Na}^{+}$ reabsorption in renal proximal tubules, KCNE1 plays a role in $\mathbf{Na}^{+}$ and substrate reabsorption in proximal parts of small intestine. However, we are not able to detect a specific immunofluorescence, possibly due to an amount of KCNE1 protein below our detection limit (79). In contrast to immunofluorescence, Northern blot analysis reveals an expression of KCNE1 in rat duodenum (70). Such a role of KCNE1 in duodenal $\mathbf{Na}^{+}$-coupled transport together with the aldosterone-stimulated $\mathbf{K}^{+}$ se-
creatin in distal colon could explain the combined fecal loss of Na\(^+\) and K\(^+\) in knockout mice. Theoretically, an enhanced Na\(^+\)/H\(^+\) content of pancreatic/intestinal secretion could also cause the increased fecal Na\(^+\)/H\(^+\) loss. Thus far, however, there is no experimental evidence supporting this hypothesis.

**KCNE1 IN AIRWAY EPITHELIUM**

There is controversy in discussions of expression and function of KCNE1 in airway epithelium. In two studies a basolateral K\(^+\) conductance (35) activated during regulatory volume decrease (44) is reported to be KCNE1 dependent. In contrast, we find no expression of KCNE1, but do find KCNE3, in murine trachea. In KCNE1 knockout mice, electrogenic cAMP-mediated Cl\(^-\) secretion, which requires basolateral K\(^+\) channels to provide the driving force, is higher in KCNE1 knockout mice (22, 32). Na\(^+\) reabsorption via epithelial Na\(^+\) channels is slightly higher in KCNE1 knockout mice. One possible explanation for these differences might be the altered hormone status after KCNE1 gene disruption, i.e., the enhanced aldosterone concentration (3). We conclude from these data that, at least in mouse trachea, Cl\(^-\) secretion and Na\(^+\) reabsorption do not require KCNE1.

**GASTRIC ACID SECRETION REQUIRES KCNQ1 BUT NOT KCNE1**

KCNQ1 mRNA is abundant in gastric mucosa (16, 80), suggesting a possible role of KCNQ1 for gastric ion transport. Interestingly, KCNQ1 colocalizes with the gastric H\(^+\)-K\(^+\)-ATPase in the tubulovesicular system of the luminal membrane compartment (20, 31). Inhibition of KCNQ1 by the chromanol 293B almost completely abolishes acid secretion (31), and the KCNQ1 gene disruption leads to a loss of acid secretion and gastric hyperplasia in knockout mice (41). These results indicate a crucial role of KCNQ1 for luminal K\(^+\).

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Table 1. Expression and putative function of KCNE1 in different mouse tissues and corresponding human pathology

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Expression</th>
<th>Localization</th>
<th>Function</th>
<th>Mouse Phenotype</th>
<th>Human Pathology of JLNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>+++</td>
<td>conductive system, sinus node, ventricle</td>
<td>repolarization of heart action potential</td>
<td>impaired QT-RR adaptability (13, 16, 25, 34, 40, 53)</td>
<td>long QT syndrome, torsades de pointes arrhythmia (51, 73)</td>
</tr>
<tr>
<td>T leukocytes</td>
<td>+</td>
<td>thymus</td>
<td>maturation?</td>
<td>accumulation of mature T cells (5, 12, 22)</td>
<td>unknown</td>
</tr>
<tr>
<td>Inner ear</td>
<td>++</td>
<td>marginal cells of the stria vascularis and vestibular dark cells</td>
<td>K(^+) secretion into endolymphatic space</td>
<td>collapse of the endolymphatic space, deafness, Shaker-Waltzer behavior (43, 46, 47, 59)</td>
<td>bilateral deafness, partially compensated vestibular dysfunction (30, 73)</td>
</tr>
<tr>
<td>Trachea</td>
<td>−†</td>
<td>unknown</td>
<td>−†</td>
<td>no (22, 32, 35, 44)</td>
<td>unknown</td>
</tr>
<tr>
<td>Gut</td>
<td>+</td>
<td>duodenum</td>
<td>substrate reabsorption?</td>
<td>fecal Na(^+) and K(^+) loss, hypokalemia, increased colonic amiloride effect (3, 22, 79)</td>
<td>unknown</td>
</tr>
<tr>
<td>Pancreas</td>
<td>†</td>
<td>unknown</td>
<td>repolarization</td>
<td>inhomogeneous distribution of secretory granules, impaired repolarization of acinar cells (16, 39, 79)</td>
<td>unknown</td>
</tr>
<tr>
<td>Submandibulary gland</td>
<td>++</td>
<td>ducts</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Stomach</td>
<td>+</td>
<td>unknown</td>
<td>no</td>
<td>no (22, 31, 70)</td>
<td>unknown</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>+</td>
<td>zona glomerulosa</td>
<td>regulation of aldosterone secretion</td>
<td>hyperaldosteronism, increased K(^+) sensitivity, hypokalemia (3)</td>
<td>plasma K(^+) usually in the normal range (72); however, occurrence of torsades de pointes arrhythmia during hypokalemic phases is increased (26, 58)</td>
</tr>
<tr>
<td>Kidney</td>
<td>++</td>
<td>brush border of proximal tubules</td>
<td>repolarization during substrate reabsorption</td>
<td>urinary salt, water, and glucose loss, hypokalemia, hemococoncentration (22, 66, 70, 74)</td>
<td>unknown</td>
</tr>
<tr>
<td>Uterus</td>
<td>+</td>
<td>endometrium</td>
<td>unknown</td>
<td>normal fertility (27, 29, 66)</td>
<td>unknown</td>
</tr>
<tr>
<td>Testis/ovary</td>
<td>++</td>
<td>unknown</td>
<td>unknown</td>
<td>normal fertility (16)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

*Expressed in mouse but not in human tissue. †Discussion of finding is controversial.

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* → †, Increasing degree of expression; −, no expression. Nos. in parenthesis are Ref. nos. JLNS, Jervell and Lange-Nielsen syndrome.
recycling during acid secretion. In rodent stomach KCNE1, -2, and -3 (all putative KCNQ1 β-subunits known so far) are expressed, with the highest levels of expression for KCNE2 (20, 22, 31, 70). Localization of KCNE2 in parietal cells by in situ hybridization (20) and activation of KCNQ1/KCNE2 channels by acidic extracellular pH (31), cAMP, and inositol 1,4,5-trisphosphate/Ca$$^{2+}$$ (unpublished data) make KCNE2 the likely β-subunit of KCNQ1 in parietal cells. We exclude a major role of KCNE1 for H$$^+$$ secretion in rodents because the KCNE1 gene disruption neither reduces acid secretion nor changes the effect of the KCNQ1 inhibitor 293B (31). In human stomach KCNE1 is not expressed, supporting the hypothesis that KCNE2 and/or KCNE3 coassemble with KCNQ1 to form the luminal K$$^+$$ conductance of parietal cells.

**KCNE1 KNOCKOUT MICE ACCUMULATE MATURE T LYMPHOCYTES**

In mouse thymus both KCNE1 and KCNQ1 are weakly expressed. They are not detected in this tissue by PCR techniques using 32 cycles (Fig. 2) but are detected with 40 cycles (12). Interestingly, KCNE1 gene disruption leads to accumulation of mature T cells in thymus and peripheral lymphoid tissue of adult mice. However, the molecular mechanisms underlying this accumulation and the possible functional modulation of the immune system by KCNE1 need to be elucidated (12).

**CONCLUSIONS**

The KCNE1 knockout mouse displays a very complex phenotype arising from direct effects due to the loss of the KCNE1 protein and due to indirect compensatory mechanisms (Table 1). In most tissues KCNE1 probably coassembles with KCNQ1; however, one has to be aware of other partner proteins. In heart muscle the loss of KCNE1/KCNQ1 (6, 61) and KCNE1/KCNH2 (4, 48) interaction, leaving homeric KCNQ1 and KCNH2 (HERG) channels behind (or these channels associated with alternative partners), might explain the pronounced QT-RR adaptability.

Like patients suffering from homozygous KCNE1 mutations (JLNS), the mice are profoundly deaf. In addition, knockout mice suffer from severe disturbance of the vestibular system, showing head bobbing and bidirectional circling (Shaker-Waltzer behavior). In JLNS patients other K$$^+$$ channels and/or secondary mechanisms probably largely compensate for vestibular defects.

Concerning the cardiac phenotype, the KCNE1 knockout mouse is an interesting animal model for JLNS, offering the possibility of extensive physiological and pharmacological experiments. Despite the fact that there are evident limitations of this model, which are mostly due to species differences in terms of heart rate, heart size, and different levels of expression of ion channels, the KCNE1 knockout mouse can help to obtain new insights in pathophysiology and disease-related phenomena.

The data on renal ion and glucose transport suggest a functional coupling of Na$$^+$$ and glucose reabsorption to a luminal KCNE1-dependent K$$^+$$ conductance. Because many transport mechanisms in small intestine are similar to those in renal proximal tubules, the KCNE1 knockout mouse can be a useful tool to investigate the possible role of KCNE1 for duodenal glucose and amino acid reabsorption.

The new observations on the role of KCNE1 for aldosterone secretion in glomerulosa cells and plasma K$$^+$$ homeostasis might be of great importance for the treatment of JLNS patients because life-threatening torsades de pointes arrhythmia often occurs during hypokalemia. These patients could benefit from a slight increase in plasma K$$^+$$, i.e., via administration of spironolactone.

The present studies on the KCNE1 knockout mouse have provided new knowledge on the pathophysiology of a gene whose human disease correlate was supposed to be well understood. These findings and future studies will help to gain a more comprehensive understanding of KCNE1 physiology and perhaps a gene-specific treatment of patients.

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