POTASSIUM CHANNELS AS A NOVEL TARGET IN THYROID DISEASES

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\textbf{ABSTRACT}

Voltage gated Potassium channels has long been recognized as important for function of excitable cell such as electrical signalling in the brain and rhythmic beating of the heart. These cells generate action potentials, which require voltage-gated sodium (NaV) channels for the depolarization phase (upstroke) and voltage-gated potassium (KV) channels for the repolarization phase (downstroke). Recently, ion transporters have been demonstrated on basolateral part of thyrocytes. Potassium channel subunits KCNQ1 and KCNE2, form a thyroid-stimulating hormone (TSH)–stimulated, constitutively active, thyrocyte K+ channel required for normal thyroid hormone biosynthesis and are essential for iodine trapping by Na+/I- symporter (NIS). This has led to new areas of intervention and opened new targets for treatment for thyroid diseases.

\textbf{INTRODUCTION}

Thyroid hormones (TH), thyroxine (T4) and triiodothyronine (T3) are crucial for proper growth and development. Both the excess and the lack of these hormones can lead to various manifestations, some of them even fatal if not recognised early. They play an integral role in maintenance of cognitive function, body metabolism and cardiac function. In addition, iodide deficiency required for thyroid hormone synthesis manifests most severely during pregnancy when then demand for TH increases. Inability to supply the growing fetus with TH can result in fetal mortality, defect in neuronal myelination and synapse formation, retarded growth and mental retardation.

Excitable cells facilitate dynamic processes such as electrical signalling in the brain and rhythmic beating of the heart. Excitability, defined in this context as the ability to sustain action potentials, requires voltage-gated sodium (NaV) channels for the depolarization phase and voltage-gated potassium (KV) channels for the repolarization phase. For example in cardiac tissues, most prominent repolarisation phase, Phase 3, is coordinated primarily by two K_\alpha subunits: hERG and KCNQ1, which respectively generate the (fast)_h and (slow)_h repolarisation potassium currents.\textsuperscript{1,2}

\textbf{POTASSIUM CHANNELS AND THYROID DYSFUNCTION}

KCNQ1 and hERG constitute α subunits of potassium channels consisting of six transmembrane helices within which is a voltage sensor that moves after membrane depolarisation, making the channel to permit ion flux. However they do not function alone. They form complexes with KCNE β subunits, also referred to as Mink–related peptides (MiRPs).\textsuperscript{3,4} KCNE subunits are single transmembrane segment (TMS) proteins that do not pass current alone, but co-assemble with pore-forming K_\alpha subunits to regulate their trafficking, gating, conductance, regulation by other proteins, and pharmacology. (Fig 1)

KCNQ1 has a property unique among K_\alpha subunits: it can be converted to a constitutively open K+ leak channel (i.e., one that does not require membrane depolarization to open) by co assembly with the KCNE2 or KCNE3 ancillary subunits.\textsuperscript{5,6} While it is not yet known whether KCNQ1 forms leak channels in human heart with KCNE2 or KCNE3, the ability to open constitutively has been shown to facilitate functional roles for KCNQ1-KCNE complexes in non-excitable, polarized epithelia \textit{in vivo}. 
In gastric parietal cells, KCNQ1-KCNE2 channels provide an apical K⁺ recycling pathway required for gastric acidification by the apical gastric H⁺/K⁺ ATPase⁷,⁸,⁹. In the colon, basolateral KCNQ1-KCNE3 channels help provide a driving force for cAMP stimulated Cl⁻ secretion¹⁰.

Roepke et al¹¹ have found KCNQ1-KCNE2 channels in thyroid follicular cells in the basolateral membrane and their role in iodide accumulation and normal thyroid hormone biosynthesis. The Na⁺/I⁻ symporter (NIS) is responsible for the accumulation of I⁻ in thyrocytes in the first step of TH biosynthesis. I⁻ is then transported apically into the colloid in the thyroid lumen where it is organified into thyroglobulin (Tg) and subsequently incorporated into T3 and T4. NIS uses the movement of Na⁺ down its concentration gradient to accumulate I⁻ into thyrocytes. While it has previously been established that the Na⁺/K⁺ ATPase, which co-localizes with NIS at the basolateral membrane, generates this gradient by pumping Na⁺ out in exchange for moving K⁺ in¹², the pathway responsible for moving K⁺ back out of the cell has remained enigmatic. Recent findings show that KCNE2, probably primarily in complexes with KCNQ1, is required for normal I⁻ accumulation in the thyroid, suggesting that the KCNQ1-KCNE2 channel may form the aforementioned thyrocyte K⁺ efflux pathway. (Fig 2)
EVIDENCES AND CLINICAL IMPLICATIONS

Targeted disruption of Kcne2 in mice impaired thyroid iodide accumulation up to eightfold, impaired maternal milk ejection, halved milk tetraiodothyronine (T4) content and halved litter size. Kcne2-deficient mice had hypothyroidism, dwarfism, alopecia, goiter and cardiac abnormalities including hypertrophy, fibrosis, and reduced fractional shortening. The alopecia, dwarfism and cardiac abnormalities were alleviated by triiodothyronine (T3) and T4 administration. These data provide a new potential therapeutic target for thyroid disorders and raise the possibility of an endocrine component to previously identified KCNE2- and KCNQ1-linked human cardiac arrhythmias.

Subclinical hypothyroidism is also associated with prolonged QTc interval, seen with loss-off-function mutations in KCNE2 and KCNQ1. Around 13% of patients with idiopathic AF have evidence of hyperthyroidism; in one study, 62% of 163 patients reverted to sinus rhythm when treatment for hyperthyroidism returned them to a euthyroid state. Lone familial atrial fibrillation has been shown to be associated with gain-of function mutations in KCNE2 and KCNQ1.

Mutations in voltage gated potassium channels are associated with cardiac arrhythmias (KCNQ1 AND KCNE2 channels). Loss of function mutations in KCNQ1 result in long QT syndrome type 1 (LQTS 1), sub-classified as Romano-Ward Syndrome (autosomal dominant) and Jervell Lange Nielsen Syndrome (autosomal recessive). Chen et al. and Yang et al. found that gain-of-function mutations in KCNQ1 appear to underlie some cases of lone atrial fibrillation. KCNE2 mutations are associated with inherited and drug induced LQTS, classified as LQTS6. These findings along with the fact that thyroid dysfunction also is associated with the prolonged QTc interval and atrial fibrillation lead to the researchers to find the role of potassium channels in thyroid metabolism. Roepke et al. demonstrated that KCNQ1-KCNE2 channels are expressed in human and rodent thyrocytes, where they generate a TSH-stimulated, constitutively-active K+ current. They found that KCNE2- mice had cardiomegaly, dwarfism and alopecia, the findings which are known to be found in congenital hypothyroidism. They generated a hypothesis that the KCNE2- disruption lead to hypothyroidism in these mice. To prove this they found that indeed the T4 level was 2 fold decreased and thyroid stimulating hormone (TSH) was 2 fold increased in KCNE2- compared to KCNE2+ mice. Further when these KCNE2- mice were surrogated with KCNE2+ dams in pre weaning period they regained normal body weight. Conversely, pre-weaning surrogacy of KCNE2+/+ pups with KCNE2- dams resulted in mean pre-weaning body weight similar to KCNE2- pups. These data suggested the possibility that maternal TH passing through milk from wild-type dams were compensating for the defect in pups. Further when thyroid hormones were replaced in KCNE2- pups, alopecia, cardiac dilatation, body weight improved. Thus they further hypothesised that KCNE2 channels had a role in thyroid hormone synthesis. They detected KCNQ1 and KCNE2 proteins in FRTL5 cell membrane fractions and which appeared to be upregulated by TSH and its major downstream effector cAMP. They then measured endogenous currents from FRTL5 cells using patch-clamp recording in the whole-cell configuration and found that a TSH-stimulated K+ current in FRTL5 cells bore the signature linear current-voltage relationship of KCNQ1-KCNE2 channels and was inhibited by the KCNQ-specific antagonist XE991. In sum, these findings proved that KCNQ1-KCNE2 channels are expressed in human and rodent thyrocytes, where they generate a TSH-stimulated, constitutively-active K+ current.

CONCLUSION

Despite there being a long-recognized link between thyroid dysfunction and cardiovascular risk, and an awareness that THs regulate expression of K+ channels in the heart, recent discovery of a crucial role for KCNE2 and KCNQ1 in TH biosynthesis presents a novel and unexpected genetic link between thyroid dysfunction and cardiac arrhythmias. Mutations in KCNE2 and/or KCNQ1 have previously been associated with LQTS, AF, and even early-onset myocardial infarction, each of which is also predisposed to by thyroid dysfunction in the general population, suggesting the intriguing possibility of an endocrine component to some KCNE2- and KCNQ1-associated human cardiac disease. Whether or not the discovery of KCNQ1-KCNE2 in the thyroid and its role in TH biosynthesis leads to use of KCNQ1-KCNE2 modulators to treat thyroid dysfunction remains to be seen, but these findings should at least be a consideration in future studies of thyroid-related cardiac disease, its molecular etiology and therapy.

REFERENCES

2. Trudeau, M. C., Warmke, J. W., Ganetzky, B., and Robertson, G. A. Science 1995;69:92-95
6. Tinel N, Diochot S, Borsotto M, Lazdunski M et al. KCNE2 confers background current characteristics to the cardiac KCNQ1 potassium channel. EMBO J 2000;19:6326-30


