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Pharmacogenetics of cardiac K^+ channels

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Abstract

A number of commonly prescribed drugs belonging to various therapeutic classes (antiarrhythmic, antibiotic, antifungal, antihistamine, antipsychotic, prokinetic drugs...) possess, in common, the adverse property to prolong cardiac repolarization [prolonged QT interval duration on surface electrocardiogram (ECG)], exposing patients to a risk of torsade-de-pointes arrhythmias, syncope, and sudden death. Arrhythmias related to drug-induced QT prolongation do not occur in every patient treated with these drugs but most likely occur in a subset of susceptible patients. These patients have a high risk of recurrence of arrhythmias upon exposure to any of the other drugs that broaden the QT interval. It is currently suspected (though not yet proven) that susceptible individuals carry a silent mutation in one of the genes responsible for the congenital long QT syndrome. Indeed, it appears more and more clear that a large proportion of congenital long QT syndrome gene carriers, have a normal QT interval and a normal phenotype and therefore, remain undiagnosed. Therefore, a much larger than previously thought proportion of the general population may be affected by asymptomatic mutations in cardiac ion channel encoding genes. No routine technology is currently available in identifying these patients preventively.

Keywords: Long QT syndrome; K^+ channel; Pharmacogenetics; Heart

1. Introduction

One of the undesirable secondary effects of many pharmacological agents is to prolong cardiac repolarization, exposing patients to a risk of paroxystic ventricular arrhythmias and sudden death. This risk is increased by bradycardia and/or hypokalemia and in patients with unidentified congenital long QT syndrome. This potentially lethal prolongation of cardiac repolarization identified for an increasing number of pharmacological agents already on the market is related to their ability to block one of the numerous outward ion currents that govern cardiac repolarization.

In the beating heart, the membrane potential depolarizes and then repolarizes at every cycle. A fine balance of inward (depolarizing) and outward (repolarizing) ionic currents tune repolarization. Inward currents are brought by a flux of positive charges entering myocytes, whereas outward currents are brought by a flux of positive charges out of the myocytes (Escande and Standen, 1993). Depolarization occurs when the sum of inward and outward currents is in the inward direction, whereas repolarization occurs when the sum of inward and outward currents is in the outward direction. Therefore, a prolonged repolarization reflects either a decrease in an outward current (the sum is less outward) or an increase in an inward current (the sum is more inward). A drug that prolongs repolarization either partially blocks one of the many outward currents that produce repolarization, or inversely (albeit most rarely), activates an inward current (e.g. an Na^+ or a Ca^{2+} current). Outward currents are mainly K^+ or Cl^- currents (an inward flux of negative anionic charges is equivalent to an outward flux of positive cationic charges). By far, K^+ currents are predominant outward currents in the heart muscle. These K^+ currents are underlain by a variety of K^+ channel proteins encoded by many genes. It is likely that the human genome comprises no more (but not less) than 74 different genes encoding for K^+ channel proteins with at least 20 K^+ channel proteins being expressed in the heart muscle. Diversity of K^+ channel proteins is remarkable in various genomes. The *Caenorhabditis elegans* genome (The C. elegans Sequencing Consortium,

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1998) which comprises six chromosomes and only 19,000 genes (the human genome is forecast to contain 35,000 to 80,000 genes), contains no Na^+ channel, seven Ca^{2+} channel, six Cl^- channel but as many as 80 K^+ channel encoding genes. The 20 K^+ channel proteins expressed in the heart muscle represent as potential targets for drugs that prolong repolarization.

Pharmacological drugs that inhibit cardiac repolarizing ionic currents prolong the time during which the heart muscle stays in a depolarized state during the action potential. Clinically, this pharmacological effect is detected by a prolongation of the QT interval on the surface electrocardiogram (ECG) and therefore represents a major cause of the acquired long QT syndrome. Because the normal QT duration adapts to changes in the heart rate, the QT duration should be normalized to the rate using correction formula (corrected QT). Cardiac repolarization is stated as being prolonged when the corrected QT duration (QTc) exceeds 440 ms. Although arbitrary, this value is often considered as a cut-off separating normal from abnormal. Prolonged QT reflects an increased risk of incidence for a peculiar ventricular arrhythmia called torsade-de-pointes. Torsade-de-pointes arrhythmia, as first described in 1966 by Dessertenne (1966), is characterized by twisting morphology of the QRS spikes around the isoelectric line. It produces tachycardia with a ventricular rate between 200 and 240 beats/min leading to impaired hemodynamical status and syncope. Although torsade-de-pointes is clearly distinct from ventricular fibrillation and is usually transient, in a number of cases, this arrhythmia can degenerate into ventricular fibrillation and cause sudden death. Therefore, drugs that inhibit repolarizing currents create a risk of sudden death in treated individuals.

2. The acquired long QT syndrome

Several drugs intentionally inhibit prolong cardiac repolarization. These drugs are used as antiarrhythmic agents and belong to the class IA (e.g. quinidine) or class III (e.g. sotalol) of the Vaughan-Williams classification based on the effects of drugs on the morphology of the cardiac action potential (Vaughan-Williams, 1984). As a matter of fact, prolonged cardiac repolarization represents both a pro-arrhythmic and an antiarrhythmic mechanism. That class IA and class III drugs may induce torsade-de-pointes has been recognized for long (Selzer and Wray, 1964; Roden et al., 1986). Torsade-de-pointes typically occur at usual or low doses and serum drug levels and may occur after months of uncomplicated drug treatment without the appearance of other known inciting factors (i.e. hypokalemia and/or hypomagnesemia).

It was also known that other pharmacological agents not belonging to the antiarrhythmic class of drugs were able to produce QT prolongation and torsade-de-pointes (e.g. bepridil or psychotropes) (Wooltorton and Mathie, 1993; Hohnloser, 1997). The issue of drug-induced arrhythmias evolved with the discovery that daily-prescribed drugs such as antihistamine agents (e.g. astemizole or terfenadine) (Zhou et al., 1999) were responsible in a limited number of cases for torsade-de-pointes. Although the incidence of such accidents is extremely low, the number of patients treated with these agents is very high and the risk/benefit ratio unacceptable for those few patients presenting delayed repolarization. Later on, different lists of drugs potentially at risk for prolonged QT and torsade-de-pointes have been issued (see Table 1 or http://www.dml.georgetown.edu/depts/pharmacology/torsades.html and http://www.fenichel.net/QT%20stuff/pqt_prolongation.htm). The bias of these lists is that they compile drugs with very different levels of risk. At least, they demonstrate that numerous drugs (belonging to different therapeutic and chemical classes) already on the market share the same side effect.

Although the K^+ currents participating to repolarize the human heart muscle are diverse (see above), it appears that the vast majority of QT prolonging drugs, do so by blocking the voltage-activated I_{Kr} K^+ current. Among 25 drugs for which a mechanism of action has been elucidated, 24 are I_{Kr} blockers. I_{Kr} is rapidly activated by depolarization during the action potential and thereafter participates to repolarization. At the molecular level, I_{Kr} is carried by HERG (human ether-à-go-go related gene) K^+ channel proteins (Sanguinetti et al., 1995). Drugs like bepridil (Chouabe et al., 1998), cisapride (Walker et al., 1999), ketoconazole (Chen and Woosley, 1993), sertindole (Rampe et al., 1998), astemizole (Salata et al., 1995), terfenadine (Salata et al., 1995), or amitriptyline (Teschemacher et al., 1999), are targeted to HERG proteins.

Arrhythmias related to drug-induced QT interval prolongation do not occur in every treated patient but most likely occur in a subset of "susceptible" patients. Susceptible patients have a high risk of recurrence of this arrhythmia upon exposure to any of the other drugs, which broaden the QT interval. It has been suggested that arrhythmias may occur preferentially in patients carrying a silent mutation in one of the different genes responsible for the congenital long QT (LQT) syndrome. As a matter of fact, the clinical diagnosis of the LQT syndrome is often hampered by age/sex influences on the QT duration (Rautaharju et al., 1992; Lehmann et al., 1997). Also, it is known that the QT interval duration and the morphology of the T wave remarkably vary depending on the locus involved (Roden et al., 1996) and depending on the mutation within the same locus (Donger et al., 1997). In addition, some LQT families exhibit a low penetrance (Priori et al., 1999), with up to 70% of LQT gene-carriers having normal QTc interval. Due to the phenotypic heterogeneity of the disease and also to the age-related attenuation of its severity in males (Locati et al., 1998; Lande et al., 2000), an unexpected large number of genetically

Table 1
List of compounds interfering with cardiac repolarization. TdP is torsade-de-pointes

Drug	Drug class/usage	Reported TdP	Prolongs QT	Blocks HERG	Off market	Labelling warning
Amitriptyline	Antidepressant	+		+		+
Astemizole	Antihistamine	+		+	+	+
Bepridil	Ca channel antagonist	+	+	+		+
Chlorpromazine	Vomiting	+				+
Cisapride	Prokinetic	+	+	+	+	+
Clarythromycin	Antibiotic	+		+		
Clemastine	Antihistamine	+				+
Desipramine	Antidepressant	+	+			+
Diphenhydramine	Antihistamine	+		+		+
Doxepin	Antidepressant	+				+
Droperidol	Agitation	+				
Erythromycin	Antibiotic	+	+			+
Fexofenadine	Antihistamine	+				
Grepafloxacin	Antibiotic	+			+	
Halofandrine	Antimalarial	+	+			
Haloperidol	Agitation	+	+	+		+
Hydroxyzine	Antihistamine					
Imipramine	Antidepressant	+		+		+
Indapamide	Diuretic	+	+			+
Ketanserine	5HT antagonist	+				
Mibefradil	Ca channel antagonist	+		+	+	
Pentamidine	Antiinfective	+	+			+
Pimozide	Seizure	+	+			+
Probucol	Cholesterol	+	+			+
Quetiapine	Antipsychotic		+			
Risperidone	Antipsychotic		+			+
Sertindole	Antipsychotic	+		+		
Sparfloxacine	Antibiotic	+	+			
Tamoxifen	Breast cancer		+			+
Terfenadine	Antihistamine	+	+	+	+	+
Terodiline	Antispasmodic	+		+		
Thioridazide	Antipsychotic	+	+	+		+

affected individuals may remain undiagnosed (Priori et al., 1999). These silent gene carriers are probably at high risk for developing torsade-de-pointes when exposed to one of the many drugs that adversely prolong repolarization. Accordingly, silent gene carriers require prevention therapy similar to those with longer QTc intervals (Vincent et al., 1999). It is the aim of pharmacogenetics to study the hereditary basis for differences in a population's response to a drug.

3. The congenital long QT syndrome

The early description of the congenital long QT syndrome has been achieved in the early 1960s by Jervell and Lange-Nielsen (1957) and by Romano et al. (1963) and then by Ward (1964). The phenotype of both the Jervell and Lange-Nielsen (JLN) and Romano–Ward (RW) LQT syndrome is characterized by a prolonged QT duration on surface ECG and by an abnormal T wave morphology. The major differences between the JLN and the RW syndromes are (i) the transmission mode of the genetic disorder: the JLN syndrome is transmitted as an autosomal recessive trait, whereas the RW syndrome is transmitted as an autosomal dominant trait and (ii) deafness which associates with a long QT phenotype in the JLN syndrome but not in the RW syndrome. However, few cases of recessive transmission have also been reported in the case of RW syndrome (i.e. biallelic mutations that are not associated to deafness).

For as yet unknown reasons, syncope does not occur in every affected individual within the same family. For those experiencing syncope, the mortality rate has been evaluated at around 50% within the 1st year in the absence of treatment. Even if not precisely known, the prevalence of the LQT syndrome in the general population has been estimated at around 1 per 8000 inhabitants in developed countries. RW syndromes are by far more frequent than JLN syndromes (RW syndrome represents about 90% of total LQTS).

As with the acquired long QT syndrome, the congenital long QT syndrome can be caused by mutations that produce either a gain of function on Na^+ or Ca^{2+} currents or inversely, a loss of function on K^+ currents. The mutated gene does not necessarily encode for the channel protein itself (the α-subunit) but may encode for an associated

regulator protein (the β-subunit) or an element of a regulatory cascade (i.e. g-protein or second messenger).

Molecular genetic approach including linkage analysis performed in large families have identified five loci responsible for the long QT syndrome. The first locus (LQT1) identified in 1991 has been assigned to the short arm of chromosome 11 (11p15.5) by Keating et al. In 1995, three other loci have been identified on chromosome 7 (LQT2; 7q35-36; Sanguinetti et al., 1995), chromosome 3 (LQT3; 3p21-24; Wang et al., 1995) and on chromosome 4 (LQT4; 4q25-27; Schott et al., 1995). In 1997, a fifth locus (LQT5) has been recognized on chromosome 21 (LQT5; 21q22; Splawski et al., 1997). However, several affected families cannot be assigned to any of these 5 loci, suggesting that the heterogeneity of the genetic LQT syndrome is even greater that previously thought. The relative importance of each the five identified loci is not equivalent with a strong over representation of LQT1 (more than 50%).

The LQT1 RW syndrome is related to monoallelic mutations in *KCNQ1*, a gene encoding KvLQT1 K^+ channel α-subunit, which, in association with IsK, generates the IKs native cardiac current. LQT5 is associated with mutations in *KCNE1*, the gene encoding IsK. At the homozygous state, biallelic mutations in the same genes may lead to the Jervell and Lange-Nielsen syndrome. LQT2 is related to mutations in the *KCNH2* gene encoding HERG K^+ channel α-subunit, which produces IKr. LQT3 is related to mutations in *SCN5A*, a gene encoding a Na^+ channel α-subunit, which is specifically expressed in cardiomyocytes. No gene related to LQT4 has yet been identified.

3.1. LQT1 and LQT5: KCNQ1 and KCNE1 genes

In the heart muscle, the KvLQT1 (encoded by *KCNQ1*) and IsK (encoded by *KCNE1*) proteins associate to create the slow delayed rectifier IKs current which was first described in Purkinje fibers (Noble and Tsien, 1969) and then further elucidated in guinea pig isolated cardiac myocytes (Sanguinetti and Jurkiewicz, 1990). Experimental data suggest a role for IKs in the shortening of the action potential duration in relation to increased heart rates.

The two components (KvLQT1 and IsK) underlying the IKs current are very different, both in structure and function (Barhanin et al., 1998). Conversely to other K^+ channel genes that were identified by sequence homologies or functional expression, the *KCNQ1* gene encoding the KvLQT1 channel protein was identified by positional cloning on chromosome 11p15.5 as the gene responsible for the LQT1 syndrome (Wang et al., 1996). KvLQT1 (676 amino acids) bears the classical structure of K^+ channel proteins with six transmembrane segments including a positively charged forth domain (S4) involved in the voltage sensing, and the P-domain signature that plays a major role in the formation of the K^+ selectivity filter. KvLQT1 subunits assemble as tetramers to form the channel that also associates with the IsK subunits. KvLQT1 is prominently expressed in the human heart as well as in the kidney, adrenal and thyroid glands, pancreas, placenta, lungs and in the *stria vascularis* of the inner ear. By contrast, IsK is a small protein (129 amino acids in humans) with a single transmembrane segment and no P domain (Barhanin et al., 1998). IsK transcripts are present in the heart, kidney, thymus, eye, ear and uterus. IsK has unique properties of interaction with KvLQT1 and serves as its essential modulator. In the heart, IsK is abundant in sinoatrial node but less abundantly expressed in ventricular myocytes. In mammalian cells, heterologous expression of KvLQT1 alone produces a rapidly activating and slowly deactivating outward K^+ current that has not been observed in cardiac cells. When expressing IsK alone in mammalian cells, no specific current can be discriminated. Co-expression of those two subunits evoke a slow time dependent outward K^+ current with very slow activation and deactivation kinetics, a small single channel conductance and a regulation by protein kinase C and intracellular Ca^{2+}. All these properties correspond to those that characterize the cardiac I_{Ks} current. Therefore, with the cloning and functional expression of KvLQT1 and IsK, not only the molecular nature of the I_{Ks} channel was elucidated, but also its role in cardiac repolarization and the lack of protection against arrhythmias featuring its loss in LQTS.

KCNQ1 is a very huge gene (more than 300 kb) and at least 120 distinct mutations responsible for LQT1 have already been described. They are mostly missense mutations located in the S2–S3, S3–S4 loops, the P domain, the S6 segment and in a conserved sequence of the C-terminal tail. Only few mutations are found in the small *KCNE1* gene (the coding sequence is only ~400 bp long) that characterize the LQT5. The most common D76N mutation concerns the cytoplasmic C-terminal segment proximal to the transmembrane domain.

Due to the large panel of both KvLQT1 and IsK expressions, mutations may not only affect the cardiac function but other functions as well. A good example is the sensorineural deafness displayed by patients with JLN syndrome, who not only exhibit a long QT interval, but also a profound deafness from birth. This results from the expression of the corresponding proteins KvLQT1 and IsK in the inner ear, where they control the endolymph homeostasis (Neyroud et al., 1997).

In most cases, mutant KvLQT1 proteins fail to produce functional channels. In less frequent occasions, the mutations encode functional channels with altered gating properties, likely to correspond to a milder clinical phenotype (Chouabe et al., 1997; Shalaby et al., 1997; Wollnik et al., 1997). The deafness characterizing JLN patients results from an almost total suppression of the IKs current in inner ear that is achieved only in the homozygous state, thus explaining the recessive mode of JLN syndrome transmission. The cardiac symptoms of those patients are also very severe. In the case of RW syndrome that is

inherited as a dominant trait, affected individuals possess one mutated allele and one wild-type allele. When co-expressed with wild-type KvLQT1 channels, KvLQT1 mutants strongly decrease the resulting currents in all RW mutations while the dominant-negative effect is very mild for the JLN recessive mutations (Chouabe et al., 1997; Wollnik et al., 1997). The picture is even more complicated when one considers that at least two KvLQT1 isoforms are expressed in the human heart (Demolombe et al., 1998): a long isoform (isoform 1) that forms the channel itself and a N-terminus truncated isoform (isoform 2) that exerts strong dominant-negative effects on isoform 1, even in healthy hearts. Thus, in cardiac cells, the amplitude of the IKs current depends on the relative expression of both isoforms. The vast majority of the *KCNQ1* mutations described to date concern segments that are common to both isoforms. Therefore, a given mutation may result in a loss of function of the channel protein (isoform 1) but also in a loss of function of its dominant-negative isoform (isoform 2). These two opposite effects are likely to be dependent of each specific mutation and to be related to their clinical severity (Mohammad-Panah et al., 1999).

3.2. LQT2: KCNH2 gene

The role of IKr in the process of cardiac repolarization and the genesis of LQT syndrome had long been suspected since drugs targeted to IKr have the potential to both prolong the action potential duration and to induce torsade-de-pointes in animal models (Salata and Brooks, 1997). In 1995, the key link between a mutated KCNH2 gene encoding HERG channel and LQT2 has been established. The HERG K^+ channel is a human homologue of the Drosophila ether-à-go-go (eag) gene, mapped to chromosome 7q35-36 (Curran et al., 1995; Sanguinetti et al., 1995). Like KvLQT1, HERG protein has the typical six-membrane spanning segments Shaker-related structure. Originally cloned from a human hippocampal cDNA library. HERG expression is prominent in the heart, and is present in the brain, retina, adrenal glands, lungs and thymus; its physiological role in those tissues remains unclear.

The IKr current is characterized by a rapid and voltage-dependent inactivation (Sanguinetti et al., 1995) that is more rapid than the activation. At positive potentials, inactivation predominates. The inactivation process being almost instantaneously removed upon repolarization, study of native IKr in cardiomyocytes, usually relies upon the measurement of its tail currents. Inversely to IKs, the amplitude of IKr decreases when external K^+ concentration decreases. This behavior has been used in the treatment in LQT2 patients with K^+ intake that has shown to correct some electrocardiographic abnormalities.

Mutations in *KCNH2* have been shown to induce an autosomal dominant RW syndrome in six families affected with congenital LQT syndrome (Curran et al., 1995). Many other mutations have since been found. All mutations induce a loss of function that results in a decrease of the IKr current that often exceeds the expected value of 50% for a simple haplo-insufficiency (Sanguinetti et al., 1996). This is caused by a dominant-negative effect of the mutated channel subunit, i.e. the inhibition of the activity of the unaffected subunits after co-assembly into heterotetramers. The severity of the mutations appears to be variable from no dominant-negative effect (the mutated subunit does not interfere with its wild type counterpart resulting in the loss of 50% of the channels) to full dominant-negative effect, in which only one mutated subunit is sufficient to impair the heterotetrameric channel, resulting in the loss of function of 95% of the channels (Sanguinetti et al., 1996). This is probably accounting for the large clinical disparity of the phenotype of patients affected by LQT syndrome.

3.3. LQT3: SCN5A gene

The *SCN5A* gene encodes for a Na^+ channel α-subunit that conducts the inward depolarizing Na^+ current responsible for the upstroke of the action potential (phase 0). Eight different genes encoding for Na^+ channels have been identified. *SCN5A* is specifically expressed in the heart. A significant proportion of the Na^+ current that does not inactivate during the action potential leads to a small inward current. Together with the inward Ca^{2+} current, this Na^+ current participates to maintain the plateau phase of the action potential (Roden and George, 1996).

SCN5A encodes for a 2016 amino acid protein made up of four homologous domains each containing six transmembrane segments and one P-domain. In that respect, the Na^+ channel α-subunit resembles an assembly of linked voltage-gated K^+ channel tetramers. Like voltage-gated K^+ channel, each of the four repeats that form the channel α-subunit contains an S4 segment acting as a voltage sensor. Although the amino acid sequence markedly differs from that of the K^+ channels, the Na^+ channel P-loop is highly conserved among species- and tissue-specific isoforms. As such, the P-loop regions in each domain are involved in defining permeation characteristics of the channel pore.

Localization of the *SCN5A* gene on locus 3p21-23 and its specific expression in the heart have made *SCN5A* a candidate gene for LQT3. *SCN5A* mutations linked to LQT3 have been identified that reduce the stability of inactivation, increasing thereof the amount of inward Na^+ current available during the plateau (Bennett et al., 1995; Dumaine et al., 1996). This effect, corresponding to a gain-of-function, causes action potential duration and QT interval prolongation. Detailed examination of the gating modifications induced by the different mutations reveals subtle distinctions. Because the cardiac Na channel plays a major role in both excitation and conduction of the im-

pulse, it is not surprising that mutations related to LQT3 would only produce minor gating modifications of the channel. This is in contrast with LQT1 and LQT2 mutations that profoundly affect the activity of the K^+ channel.

The *SCN5A* gene product is a target for numerous antiarrhythmic drugs belonging to the class I category (Roden, 1996). It is generally difficult to develop a specific therapy for loss-of-function mutations (i.e. LQT1 or LQT2). By contrast, gain-of-function mutations are accessible to classical pharmacological intervention. To that respect, the use of class IB antiarrhythmic drugs such as mexiletine or lidocaine has been proposed as a therapy for LQT3 patients. In a limited number of genotyped LQT3 patients, mexiletine normalizes the QT duration. However, this does not necessarily preclude to reducing the occurrence of torsade-de-pointes episodes.

4. Conclusions and perspectives

As yet, only four genes have been identified as responsible for the congenital long QT syndrome. Silent mutation in other cardiac ion channel (or channel regulator) encoding genes may also lead to susceptibility to the acquired long QT syndrome. In that setting, a recent report has established a correlation between mutation in a K^+ channel regulator gene (*KCNE2*) and susceptibility to drug-induced QT prolongation (Abbott et al., 1999). Many other genes have not being evaluated yet for their possible association with susceptibility. In addition, variants should not only be screened in exons but also in introns including promoter regions since susceptibility could result from a decreased expression of a repolarizing ion channel in comparison with normal. Clearly, many more research efforts remain to be accomplished before genetic susceptibility to the acquired long QT is fully understood.

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