Mechanisms and Clinical Relevance of Drug-Induced Long QT Syndrome: Block of hERG, Drug Metabolism and Drug Transport in the Human Heart

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Abstract
Long QT Syndrome (LQTS) is a serious cardiac disorder that can derive from both congenital and drug-induced circumstances. Several mechanisms have been proposed to explain drug-induced LQTS, though the blocking of hERG channels (IKr) by drugs on ventricular cardiomyocytes remains the most prevalent. The blocking of this potassium channel prevents the timely repolarization of cardiomyocytes, instead allowing for a prolonged action potential. This translates clinically on the surface ECG to a prolongation of the QT interval. Such an interruption in the normal electrophysiology of the heart can lead to proarrhythmic events, polymorphic ventricular tachycardia (Torsade de pointes; TdP), and sudden death. The aim of this review is to present an understanding of the normal electrophysiology of the cardiac ventricular myocyte, to outline properties of hERG channels, to describe the role of hERG block in the etiology of drug-induced LQTS, and offer a special and novel look at the role of drug metabolism and transport in the human heart for drugs with hERG blocking properties. Some examples of previously and currently used medications-terfenadine, pimozide, risperidone, and rosuvastatin-are described with higher likelihood of blocking the hERG channel under conditions of cardiac CYP450 inhibition or decreased cardiac drug transport. Considering the depth of knowledge about cardiac electrophysiology, drug disposition, genetics, and new bio-devices, drug-induced LQTS is reasonably preventable. Predisposing conditions should be identified by alerted pharmacists, and the use of certain medication regimens need to be addressed to ensure patient safety.

Keywords: Cardiac electrophysiology; Potassium channels; Drug-drug interactions; Long QT syndrome; Cytochrome P450; hERG

Introduction
Ventricular arrhythmias are among the most dangerous heart defects, often ranked as the leading cause of sudden cardiac arrest [1]. As such, the breadth of research done on the subject is vast. This review will focus on one often asymptomatic condition known as the "Long QT Syndrome (LQTS)". and more specifically, on recent insights into the pathophysiology of its drug-induced form (Drug-induced LQTS). Some highlights include a discussion on the blockade of a specific cardiac potassium channel protein by various drugs, as well as the role of multi-drug interactions involving drug metabolism and drug transport in the human heart as specific elements of its etiology.

Time-related variation in transmembrane voltage occurring during the depolarization-repolarization sequence of cardiac ventricular myocytes (action potential) is captured on the surface ECG by the QRS-T waves (Figures 1A, 1B). It is considered common knowledge that this sequence would become disrupted if the efflux of potassium ions from ventricular cells is obstructed following a programmed or spontaneous depolarization (Figure 2A) [2]. Under such conditions, the cellular membrane of ventricular cells takes more time to return to its resting potential (prolonged repolarization phase) [2]. This may favor conditions of premature and additional depolarizations due to a re-opening of calcium channels (Early after Depolarizations; EADs) which may lead to ventricular fibrillation, making it impossible for the heart to pump blood throughout the body.
Normal Cardiomyocyte Electrophysiology

The normal ventricular action potential electrophysiological cycle is divided into five phases (Figure 1) [19]. The cycle begins in Phase 4 when the ventricles are at rest following their previous contraction. At this point in the cycle, the membrane potential of ventricular cells is approximately -90 mV (excess of negative charges in the interior of the cells). In terms of electrogenic activity, the cell membrane is only permeable to potassium ions at this time. This selective permeability is due to the opening of specific voltage-gated inwardly rectifying potassium channel (Kir2.x) subfamily members that mediate the “inward rectifier potassium current”, namely IK1 [20].

Insert 1

Most ion channels are transmembrane proteins that are activated either by a change in voltage, by binding of a ligand (intracellular or extracellular), by mechanosensory triggers or by a change in volume. Ion channels may be specific or non-specific to certain solutes (e.g. sodium or potassium) and control the ability and rate of flow of the solutes into (influx) or out (efflux) of the cell. The movement of ions into and out of cardiac myocytes affects the heart’s electrical activity.

Cardiac cells are connected via gap junctions whereby the voltage differences can be propagated from one point through the rest of the organ. From a single impulse that originates from the sinus node, the atria, ativoventricular nodal cells, His-Purkinje and ventricular cells are depolarized in a sequential manner. As a result, major changes in ventricular cell transmembrane potential occur as a depolarizing wave enters the ventricles. This wave generates a flow of sodium ions through gap junctions and makes the membrane potential of ventricular myocytes less negative. Ventricular myocytes enter into their Phase 0 as their membrane potential reaches the threshold of -70 mV. At this point, “fast” voltage-gated sodium channels (Na\textsubscript{v}1.5) open, producing a large influx of sodium ions (less than 2 msec) and generating the rapid sodium current (INa). As the membrane voltage reaches -40 mV, slower L-type (long opening) calcium channels open (Cav1.2/1.3) and allow for the entry of calcium ions (slow inward calcium current; I\textsubscript{to1}). Combined with the rapid entry of sodium ions, this influx of calcium ions brings the membrane potential past 0 mV, where it will continue to rise to about +30 mV and the cardiomyocytes transition into Phase 1 of the cycle.

Insert 2

Voltage-gated ion channels often exist under three different conformations: CLOSE-OPEN-INACTIVATED. Statistical transition (likely hood of being under one conformation or the other) from one conformation (state) to another depends on voltage, time, temperature, other ions and the presence of drugs which may preferentially bind to one of the conformation and change its kinetics.

Two phenomena occur directly at the start of Phase 1. When the membrane potential reaches about +10 mV, Na\textsubscript{v}1.5 channels inactivate quickly and considerably reduce the rise in voltage (decrease in I\textsubscript{Na}); these channels will change conformation and close later. At the same time, the voltage-gated potassium channels K\textsubscript{v}4.2/4.3 open and generate the transient outward current (referred to as I\textsubscript{to1}) [2]. This allows potassium ions to leave the cell due to favorable electrogenic activity; the potassium, a positive charge is present in larger amounts intracellular (~150 mM) compared to the extracellular compartment (~3.5 mM) and the interior of the ventricular cell is now more positive than the exterior of the cell [2]. Consequently, with the efflux of positive charges, the transmembrane

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As the voltage of the ventricular cardiomyocyte approaches 0 mV, the efflux of potassium through I\textsubscript{\text{Kr}} tends to diminish. Phase 2 is commonly referred to as the "plateau phase" as the rate of potassium efflux (due to I\textsubscript{\text{Kr}}) and opening of other potassium channels, as described below) is equal to the rate of calcium influx, and the cell membrane remains around 0 mV for a long period (on average in the range of 150 msec). The influx of calcium from the L-type channels leads to additional calcium being released from the sarcoplasmic reticulum, called calcium-induced calcium release [21]. The release of extra calcium leads to the ultimate objective of this complex electro-mechanical activity of cardiac ventricular myocytes, namely the contraction of the ventricles and blood ejection to perfuse the organism. The L-type calcium channels then inactivate and close while some potassium channels open and Phase 3 begins.

The last phase of the cardiac cycle is where repolarization of the cardiomyocyte occurs. In addition to the I\textsubscript{\text{Kr}} channels, hERG (K\textsubscript{v11.1}) and K\textsubscript{v7.1} channels, which have started to open during Phase 2, then open much further with different activation and inactivation/closing kinetics [22]. The flow of potassium ions through hERG and K\textsubscript{v7.1} channels generates two important potassium currents, described as the rapid (I\textsubscript{\text{Ks}}) and slow (I\textsubscript{\text{Kr}}) components of the delayed rectifier [23]. The greater amount of opened potassium channels allows for a larger efflux of potassium ions, and the membrane potential quickly returns towards more negative voltages. This efflux of potassium ions is the single most important step in returning the ventricle to its resting state. Aiding in the repolarization and equilibration of the cell are the sodium-calcium ATPase and the sodium-potassium ATPase transporters.

hERG block as a major determinant of drug-induced long QT syndrome (LQTS): The congenital form of LQTS has been one of the most investigated cardiac ion channelopathies, especially in the 1990’s, when it drew a lot of attention with the identification of specific genetic variants [24-26]. More than 3 decades after the description of the autosomal recessive Jervell and Lange-Nielsen syndrome [30], since then, genetic studies have identified and characterized several other genes associated with the familial forms of LQTS were discovered in three major ion channel genes: KCNQ1 (K\textsubscript{v7.1} which generates the I\textsubscript{\text{Ks}} current), KCNH2 (K\textsubscript{v11.1}, hERG which generates the I\textsubscript{\text{Kr}} current) and SCN5A (Na\textsubscript{v1.5} which generates the I\textsubscript{\text{Na}} current) [24-29]. These variants explain about 75% of congenital forms of LQTS observed clinically [30]. Since then, genetic studies have identified and characterized several other genes associated with the familial forms of LQTS.

Cardiac disorders caused by problems associated with either ion channels or conduction pathways of the heart can lead to arrhythmias. One particular ion channel that can lead to a serious cardiac disorder is the hERG channel [23]. As indicated in the previous section, hERG proteins are expressed at the plasma membrane of cardiac ventricular myocytes [31]. These ion channels consist of four a-subunits (K\textsubscript{v11.1} protein) which can either be homomeric or heteromeric [32,33]. This protein is encoded by the human ether-a-go-go-related gene (hERG; also denoted as KCNH2) [34,35]. Four different isoforms -hERG 1a, hERG 1b, hERGuso, hERG1buso-have been identified, and all have been found distributed to varying degrees within the heart [24,36,37].

All four hERG subunits share similar structural features. Each protein has six transmembrane alpha helices (labeled S1-S6), as well as intracellular amino and carboxyl termini (Figure 3) [19]. The S4 helix contains positively-charged amino acids at every third or fourth position. These amino acids may serve as voltage sensors that regulate the state of the ion channel through conformation changes [38]. A hydrophobic "pore loop" is situated between S5 and S6 [19]. It does not completely traverse the cell membrane, but does contribute to the central ion pore’s selectivity via its interaction with the pore loops of the other subunits [19]. The N- and C-termini contain domains of the PAS domain and the cyclic Nucleotide Binding (cNBD) domain respectively, which play important roles in the trafficking of the protein to the cell membrane after modification in the endoplasmic reticulum [41].

Certain features of the S6 helix confer specific binding properties to the hERG channel. One such feature is the lack of a Proline-Proline (PxP) motif. In other potassium channels, the PxP motif produces a kink that limits the size of the pore cavity [38]. Without this PxP motif, the hERG pore cavity can be of a much larger size, and this larger pore size allows for molecules larger than potassium ions, such as drug molecules, to enter and block the pore cavity. An example of this blocking is depicted in Figure 4. Drug binding to the hERG channel is also enhanced due to the presence of aromatic amino acid side chains, specifically phenylalanine and tyrosine [38]. Phenylalanine and tyrosine can participate in cation-π and π-π interactions with drug molecules. Occupation of the pore by drug molecules will prevent the efflux of potassium ions, and therefore the repolarization of the ventricular cardiomyocyte [38].

The cardiac disorder associated with important blocking of hERG channels, and the resulting decrease in I\textsubscript{\text{Kr}} current, is drug-induced Long QT Syndrome (LQTS). Drug-induced LQTS is a relatively rare condition with a prevalence rate of 0.8 to 1.2 per million people per year [42]. Several medications have been associated with drug-induced LQTS and risk of sudden death, including antihistamines, antibiotics, antifungals, diuretics, antiarrhythmics, protease inhibitors, tyrosine kinase inhibitors, antidepressants, and antipsychotics [43]. One of the most easily recognizable symptoms of LQTS is syncope, or fainting. This occurs after a fast-polymorphic ventricular tachycardia, also known as Torsade de Pointes (TdP) [44]. If the TdP converts into...
ventricular fibrillation, and the ventricles are incapable of contracting synchronously, leading to blood stasis, then sudden death is likely to occur.

Besides blocking of hERG, the key physiological characteristics that increase the risk of drug-induced LQTS in patients with polypharmacy are bradycardia (especially a sinoatrial pause), hypokalemia, hypomagnesemia, female gender, T-wave alternants, drug-induced increased \( I_{\text{to}} \) and some genetic variants in ion channels [45]. The role of drug metabolism, drug transport, and drug-drug interactions will be discussed further below.

The beginnings of our understanding of drug-induced LQTS: In the early 1960s, an association was established between TdP and the initiation of therapy with quinidine, a drug known to prolong the QT interval [4]. This association was extended to other drugs, such as Class III antiarrhythmics (N-acetylprocainamide, sotalol, and d-sotalol), but especially to the second-generation antihistamine drug terfenadine [46,47]. Starting in 1989, cases of TdP caused by intentional overdosing of terfenadine were reported by Davies et al. [48]. Terfenadine was a blockbuster drug as the first non-sedating histamine H1-receptor antagonist available on the market, and by 1995 the time of Davies’s publishing, it had been used in clinical settings for at least ten years [48]. In 1990, Monahan et al. [49], published the first report of a patient with TdP induced from a normal dose of terfenadine. As an investigation by the FDA proved, the majority of similar cases reported resulted from an individual’s inability to properly metabolize terfenadine [50]. Factors that contributed to this inability were both liver disease and drug-drug interactions; specifically those with drugs that inhibit the functioning of the CYP3As enzyme [50]. Examples of these drugs include macrolide antibiotics, such as erythromycin and clarithromycin, as well as imidazole-containing drugs, such as ketoconazole and itraconazole.

Following these investigations, other experimental studies showed the ability of grapefruit juice to inhibit CYP3A4 and terfenadine metabolism [51]. Such conclusions pointed to the idea that the parent compound and not the metabolite were responsible for causing TdP [46]. Electrophysiological studies using the patch-clamp technique demonstrated that terfenadine had a great potency (very low IC\(_{50}\) in the nanomolar range; 16 nM) to block hERG channels in various experimental models [52]. On the contrary, fexofenadine, an active metabolite of terfenadine, was not associated with such hERG blocking properties (IC\(_{50}\) of 65 μM; more than 4,000 times less potent) [53]. Thus, conditions associated with an increase in terfenadine plasma concentrations (decreased metabolism through CYP3A inhibition) favored a block of the hERG channel in the heart, led to QT prolongation, and increased the risk of TdP.

Insert 3

The beginnings of our understanding of drug-induced LQTS: Conditions associated with an increase in plasma concentrations (decreased metabolism) for certain drugs may favor block of the hERG channel in the heart. Blocking of hERG channel proteins may lead to QT prolongation and an increased risk of TdP.

As a result of the extensive findings, terfenadine was removed from the market in 1997 and eventually replaced by fexofenadine [54]. To date, fexofenadine has not been implicated in any patient cases of drug-induced long QT and/or TdP, nor has it been associated with arrhythmogenic potential during clinical trials. This holds true even at doses higher than recommended levels or when administered concomitantly with drugs which can affect its metabolism [54].

Drug metabolism in the heart and extent of hERG binding: Studies conducted by our group have demonstrated the expression and functionality of various CYP450 isoenzymes in the human heart [55,56]. These observations support the concept that drug metabolism in an organ is a major determinant of intracellular drug concentration. Accordingly, drug metabolism in the heart may govern drug action on a protein such as hERG, which exhibits a binding site for its blocking on the intracellular side of the plasma membrane of ventricular cardiomyocytes.

Insert 4

Drug action on hERG: Drug binding site to hERG is intracellular. Therefore, factors which control intracellular concentrations of drugs such as cardiac drug metabolism or influx/eflux transport through the cellular membrane may be major determinants of drug action on this ion channel.

There are over fifty-seven different CYP genes in the human genome, and fifteen of them can be found inside the human heart [57]. Of these, CYP2J2 is the most abundant [58]. The two primary functions of CYP2J2 are the biosynthesis of epoxyeicosatrienoic acids, or EETs, and drug metabolism [55,59]. EETs play an important role in cardioprotective signaling, including within cardiomyocytes, where they act as agonists for ATP-sensitive potassium channels (K\(_{\text{ATP}}\); \( I_{\text{KATP}} \)) that contribute to the transport of potassium ions out of the cell during repolarization [60]. Solanki et al. [61] ascertained that a significant loss in CYP2J2 activity would impact the ability of the ventricular cardiomyocytes to reach their resting membrane potential.

The role of CYP2J2 in drug metabolism is just as important to cardiac function as its biosynthetic work. Drugs like terfenadine, ebastine, astemizole, pimozide, and risperidone are considered cardiotoxic because they can bind to hERG proteins, effectively blocking this voltage-gated potassium channel and therefore leading to LQTS [62]. CYP2J2 is the single biggest metabolizer of both these and other cardiotoxic drugs, both in the heart and in other organs [55].

Some observations are of great interest in our understanding of drug-induced LQTS: 1) CYP3As and CYP2J2 isozymes share several
characteristics, such that several substrates of CYP3As are also substrates of CYP2J2, including ebastine, terfenadine, astemizole, pimozide, cisapride, domperidone; [63]. 2) Several inhibitors of CYP3As are also inhibitors of CYP2J2 (macrolide antibiotics and imidazole antifungals); [64]. 3) CYP3As and CYP2J2 exhibit different patterns of relative tissue expression: CYP3As expression is liver>intestine>and heart (if any expression at all), while CYP2J2 is heart>intestine>and liver; [57]. 4) Thus, conditions associated with decreased activities for both isoforms may lead to increased blocking of hERG, due to increased intracellular concentrations of a drug with or without increases in its plasma concentration.

Demonstration of this concept can be made using data involving either pimozide or risperidone. Both antipsychotics are metabolized by CYP3A/CYP2J2 (50% of their oral clearance) and by CYP2D6 (50%) [65]. As a first example, the publication by Flockhart et al. [66], described QT prolongation and sudden death in a patient treated with pimozide and clarithromycin. With only few variant alleles tested, the patient happened to possess one non-functional CYP2D6 variant allele (CYP2D6∗1/∗4) suggesting reduced clearance through this pathway. Concomitant administration of clarithromycin further reduced the oral clearance of pimozide by inhibiting CYP3As and CYP2J2 (in the liver and intestine), increasing plasma levels that act as the driving force to increase cardiac intracellular concentrations of pimozide. In addition, concomitant inhibition of CYP2J2 in cardiac myocytes by clarithromycin could favor further increase in pimozide intracellular concentrations and produce deleterious blocking of hERG.

Even more compelling evidence of the role of cardiac CYP2J2 could be derived from a case report of significant QT prolongation with risperidone. A 37-year-old schizophrenic woman was admitted to the hospital for psychotic episodes. While her ECG results remained normal during her initial treatments, the addition of 2 mg risperidone to her daily medication regimen (benzodiazipines, aripiprazole, haloperidol, escitalopram) prolonged her QTc interval by fifty milliseconds, despite the patient having no family history of cardiac-related issues [67]. Three consecutive challenges demonstrated drug-induced QTCS with risperidone (2 mg) in the absence of elevated plasma levels of the drug or its metabolite (paliperidone), and no mutation was detected on the hERG gene to explain these effects. Challenges were performed while removing potential perpetrator drugs in a sequence. We would like to propose that increased intracellular concentrations due to local inhibition of CYP2J2, decreased CYP2J2 activity due to genetic variants, or inefficient efflux of the drug from the intra-cardiac site (see discussion below as risperidone is a known substrate of BCRP) in the absence of increased plasma concentrations, could have led to increased block of hERG (blocking of hERG channel by drugs such as risperidone is intracellular) [68].

**Drug transport in the Heart and Extent of hERG binding:** Transporters are cell membrane proteins that are involved in moving solutes (e.g., nutrients, drugs, waste) into or out of the cell [69]. There are two main families of transporters: ABC-Transporting Cassette (referred to as ABC transporters) and Solute Linked Carriers (referred to as SLC transporters). Influx transporters move the drug (or other substrates) into the cell while efflux transporters move the drug and/or its metabolites (or other substrates) out of the cell. Most efflux transporters are part of the ABC transporter superfamily, and most influx transporters are part of the SLC superfamily. Efflux transporters are one of the major mechanisms of drug resistance (especially in cancer cells), which lowers the effect of the medication. This action does prove useful, however, when the substrate is a toxin [70].

Specific transporters have been implicated in LQTS, such as P-glycoprotein (ABCB1), also known as breast multidrug resistance protein 1, and BCRP (ABCG2), also known as the breast cancer related protein [71]. For instance, in a study with romidepsin (an anticancer agent and a QT-prolonging drug), mice that lacked P-glycoprotein had higher concentrations of the drug inside the heart, leading to a higher probability of the mice developing LQTS.

One of the top 200 drugs prescribed to patients is rosuvastatin (Crestor), which is indicated for the treatment of hyperlipidemia [72]. Despite its status as a frequently prescribed and used drug, not much research has been conducted regarding possible links between rosuvastatin and drug-induced LQTS. Compositionally, rosuvastatin derives from a methanesulfonamide compound, which has been linked with LQTS due to its structural similarity to hERG blockers [16]. Using the patch-clamp technique, we demonstrated that rosuvastatin exhibits potent blocking of IKr current (hERG channels) with an IC50 of 154 nM. In one series of experiments, block of IKr by rosuvastatin was tested in cells expressing the influx transporter OATP2B1, which is known to be expressed in the human heart and transport rosuvastatin into the cell. When more rosuvastatin was taken into the cell by these influx transporters, IKr blockage was increased [16].

In another series of experiments, rosuvastatin was tested in cells co-expressing the wild-type and variant forms of the efflux transport BCRP. Functional BCRP reduced the amount of rosuvastatin within the cell and, consequently, the extent of hERG blockage observed; non-functional variant forms of BCRP had no effect. In other words, high intracellular concentrations of rosuvastatin were implicated with the blocking of the hERG protein. If a patient has over-expressed OATP2B1 influx transporters or under-expressed BCRP efflux transporters, the rosuvastatin concentration inside the cell could rise to dangerous levels that are more likely to bind to hERG proteins. This type of event leads to QT prolongation and could evolve into TdP.

**A look in to the future:** Given the well-researched nature of drug-induced LQTS, it is reasonable to assert that it is a preventable condition in today's practice, as several mechanisms have been elucidated, including the various pathways that lead to hERG blocking. Predicting whether a new drug may cause LQTS based on its chemical structure, protein conformation and binding site, in addition to the use of predictive pharmacometric modeling, is a viable option. Although retroactive safety measures, such as taking terfenadine off the market, are necessary at times, it is far more essential to educate prescribers and give them tools to assess the risks of drug-induced LQTS in their patients. With the rise of genomic testing and artificial intelligence, such assessment may become a reality, and might also include continuing education courses for practitioners, physicians and pharmacists alike. Furthermore, several bio-devices (Alivecor Kardia Mobile, Biofourmis, Cquentia) are linked to a smart phone, and can allow easy acquisition of a surface ECG and a real-time measurement of the QT interval the best biomarker of risk associated with drug-induced LQTS. This can be achieved by any healthcare professional and even by patients themselves (associated risk score/alarms).
Conclusion

Drug-induced LQTS is a relatively rare condition. Block of the hERG potassium channel protein by drugs from various pharmacological classes remains by far the most relevant predisposing factor. Conditions associated with drug accumulation in the heart such as inhibition of CYP3As or CYP2J2 isoforms, or BCRP efflux transporters could favor intracellular block of hERG and increase the risk of TdP. Identification of these factors, modulation of drug transporters could favor intracellular block of hERG and increase such as inhibition of CYP3As or

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