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COMMENTARY

Protein trafficking abnormalities: a new mechanism in drug-induced long QT syndrome

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Drug induced long QT syndrome (LQTS) can lead to cardiac arrhythmias and sudden death, and has emerged as a worldwide problem. Most drugs that cause this are thought to directly block a specific cardiac ion channel (KCNH2 or hERG) that carries the rapidly activating delayed rectifier potassium current, I_{Kr}. In this issue of the *British Journal of Pharmacology*, evidence is presented to support a new mechanism for causing drug induced LQTS. The drug pentamidine, at near therapeutic concentrations that do not cause direct KCNH2 channel block, disrupts normal KCNH2 channel protein processing and maturation to reduce its surface membrane expression. This indirect mechanism for reducing I_{Kr} is novel, and whether other drugs may cause similar protein trafficking abnormalities is largely unknown.
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Abbreviations: HEK293, human embryonic kidney cell 293; I_{Kr}, rapidly activating delayed rectifier potassium current; LQTS, long QT syndrome

Drug-induced cardiac myocyte action potential prolongation, as evidenced by a prolonged QT interval on a patient's surface electrocardiogram, can lead to the potentially lethal ventricular arrhythmia *torsade de pointes*. Although originally described for antiarrhythmic drugs such as quinidine and sotalol, drug-induced long QT syndrome (LQTS) is now known to occur with many noncardiovascular medications. Over the last 15 years, important new insights have been gained into the cellular mechanisms that cause LQTS, including the roles of triggered activity (early after depolarizations) and tissue heterogeneity of repolarization. It has also been shown that nearly all drugs that cause LQTS act by blocking directly the rapidly activating delayed rectifier potassium current, I_{Kr} (Roden, 2004), which is encoded by the *human ether-a-go-go-related gene* (*hERG* or *KCNH2*). Owing to its unique structure and drug-binding domain, the KCNH2 potassium channel pore is promiscuous in its sensitivity to block by a wide variety of drugs, and in the last decade block of KCNH2 channels has emerged as a major problem facing both pharmaceutical and regulatory agencies.

Pentamidine, an antiprotozoal agent, has been known since at least 1987 to cause QT interval prolongation. The mechanism by which this drug alters repolarization has not been previously elucidated. In this issue of *British Journal of Pharmacology*, Cordes *et al*. (2005) describe the mechanism by which pentamidine reduces I_{Kr}. These authors show that pentamidine, like many drugs, blocks KCNH2 channels stably expressed in a human embryonic kidney cell (HEK293) line, and does so in a concentration- and voltage-dependent manner. The authors suggest that block is independent of the state of the channel, which is somewhat unusual as most drugs interact preferentially with the open or inactivated states. The IC_{50} for KCNH2 channel block was 252 μM, a value nearly 500 times higher than the therapeutic free-pentamidine concentration.

This drug concentration paradox was investigated further by incubating KCNH2 channel expressing HEK293 cells in low ('therapeutic') concentrations of pentamidine. A 2-day incubation in pentamidine (1–10 μM), compared to control cells, resulted in altered growth in some cells and a decrease in KCNH2 current density of 36–85% measured by whole-cell patch clamp. The authors also performed Western blot analysis and confocal immunofluorescence imaging of control and pentamidine incubated cells, and showed in drug treated cells disruption of normal protein trafficking of KCNH2 channels with a concomitant reduction in mature KCNH2 protein. The authors conclude that the chronic administration of pentamidine causes a protein trafficking abnormality of KCNH2 channels. This work amplifies the recent report by Rampe and co-workers (Kuryshev *et al*., 2005), who also showed that low concentrations of pentamidine selectively disrupted protein trafficking and maturation of KCNH2 channels but not of hKv1.5, KvLQT1/minK and Kv4.3 channels, and that in isolated guinea pig ventricular myocytes culture in pentamidine (10 μM) prolonged action potential duration and reduced I_{Kr}. Taken together, these two papers provide clear evidence of a novel mechanism for causing drug-induced LQTS; disruption of KCNH2 channel protein trafficking to reduce surface membrane expression of functional channels.

For at least one other drug, arsenic trioxide, disruption of normal KCNH2 channel protein processing has been implicated as a mechanism for drug-induced LQTS (Ficker *et al*., 2004), although arsenic trioxide has also been reported to directly block KCNH2 channels (Drolet *et al*., 2004).

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Disruption of KCNH2 channel protein trafficking to reduce surface membrane expression of functional channels is not new. In inherited cardiac arrhythmia diseases, including congenital LQTS, defective trafficking of mutated ion channel proteins (and co-assemble subunits) has emerged as an important mechanism (for discussion, see Delisle *et al*., 2004). Furthermore, that drugs can modify ion channel protein trafficking intracellularly also is not new. In fact, for some trafficking-defective mutations in cardiac ion channels, trafficking can be improved ('rescued') by drugs that normally act as channel blocking agents, and this has therapeutic potential.

What is new in the work by Cordes *et al*. (2005) and Kuryshev *et al*. (2005) is the recognition that some drugs causing LQTS can selectively reduce I_{Kr} by disrupting protein trafficking and channel maturation, rather than by direct block of surface membrane channels. This represents a new and novel indirect mechanism for causing drug-induced LQTS, and it raises several interesting questions. (1) The site of drug interaction within a cell remains unknown. (2) It is not known if a drug-induced trafficking defect can be 'rescued' or corrected. (3) It is unknown if most 'conventional' KCNH2 channel blocking drugs can also induce defective protein trafficking. Although for the prototype antiarrhythmic drug E4031, which causes direct, high-affinity KCNH2 channel block, culture of wild-type KCNH2 channel expressing cells in E4031 is known to not affect channel expression (Zhou *et al*., 1999). (4) The finding of selective disruption of KCNH2 channel trafficking suggests that specific and separable protein processing steps may exist for different cardiac ion channel proteins. (5) In drug development, early screening of lead compounds for direct, high-affinity KCNH2 channel block is becoming commonplace, and it will now need to be considered whether indirect effects on ion channel protein trafficking will need similar screening. Finally, the present work illustrates the interplay between the drug-induced (acquired) and inherited (congenital) LQTS, where mechanisms of one disease interrelate with mechanisms of the other. Undoubtedly, drug-induced alterations in protein trafficking will assume increased importance for future study.

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