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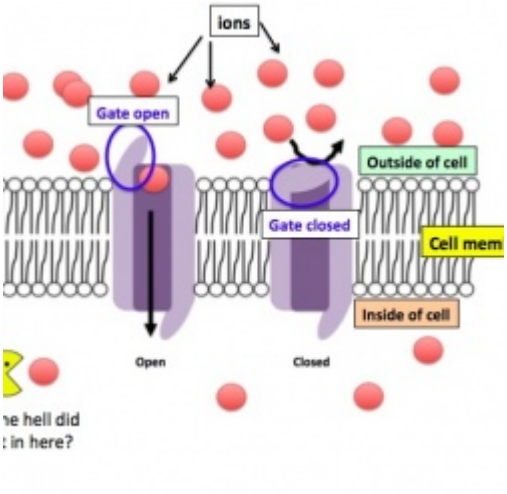
The Real Problem With Hydroxychloroquine Is Nothing New. It's Chemistry.

By Josh Bloom — May 20, 2020

Somehow a drug has turned into a political tool. This is nuts. Hydroxychloroquine may or may not end up having any utility as a COVID-fighting drug. But its cardiac toxicity is real, unlike the nonsense surrounding it. Let's stick to the science: Torsades de pointes, not talking points.



Ion Channels In Cell Membranes. And Lots of Pretty Colors. Modified from a Wikipedia image.

Sometimes science makes sense. This is a message we should not forget because we are being hit by a constant barrage of new information, theories, guesses, etc., all related to coronavirus, a bizarre pathogen that has no precedent and doesn't make much sense, at least yet.

So, it was rather comforting to read about one familiar aspect of drug discovery, an assay called hERG, which stands for (don't even try to guess) the *human ether-a-go-go-related gene* **(1)**. Because if there is anything that gives drug discovery scientists one *Mamacita* of a stomach ache it is finding out that a potential drug candidate they've been working on has a hERG problem. It's usually a show-stopper. This is such a serious issue in drug development that high-throughput screens [1] of multiple potential drugs can be run to weed out these compounds early in the process.

It is hERG that makes HCQ (and other drugs) *potentially* dangerous. And it is no coincidence that the primary concern about the drug is cardiac toxicity, specifically arrhythmias. It might even make some sense to you, assuming you can withstand a few paragraphs about voltage-gated ion channels – a topic that doesn't come up often enough at dinner parties, if you ask me. Give it a try. It's not too bad. (Figure 1)

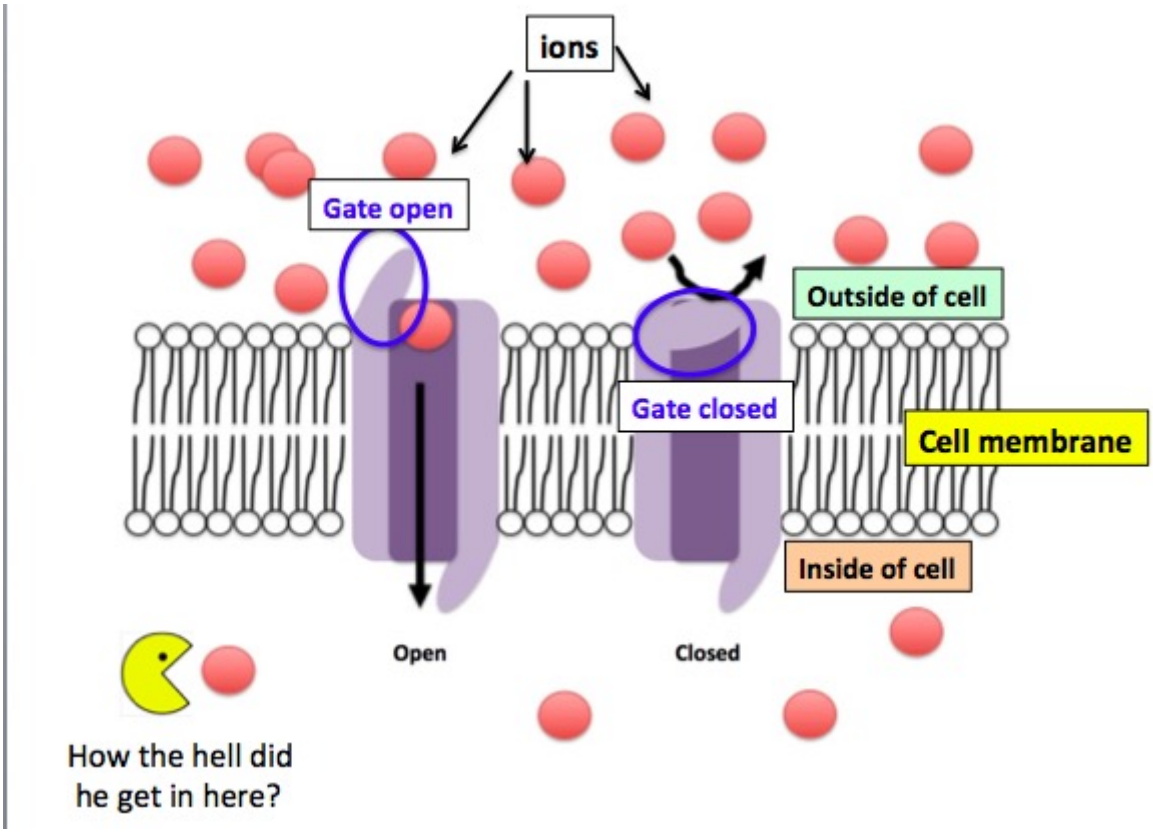


Figure 1. A simplified view of voltage-gated ion channels. Sodium, potassium, calcium, and chloride ions (all ions in this diagram are represented by red circles) move between the inside (orange) and outside (green) of cells through channels (purple cylinders) embedded in the cell membrane. This causes a tiny electric current, which forms the basis for the timing of heartbeats as well as multiple nerve-related functions. The timing of the movement of ions (in and out of cells) is controlled by the opening and closing of a gate (blue ovals).

WHAT DOES hERG HAVE TO DO WITH THIS?

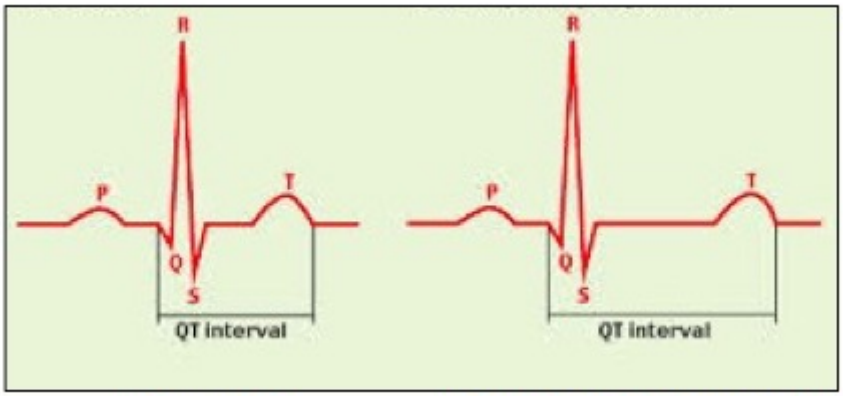
hERG is a gene that makes a protein that is part of the potassium ion channel. So, when a drug or chemical binds to the hERG protein it can block that channel, which disrupts the timing of the flow of ions in and out of the cell. The degree of binding determines the amount of disruption. Given that the heart is controlled by regular electrical impulses it should not be surprising that heart cells

have ion channels or that messing with them disrupts the timing.

What happens when the timing of your heart screws up? Arrhythmias - irregular heartbeats. If the ventricular contraction speeds up it is called ventricular tachycardia, which is something you'd be wise to leave off your Christmas wish list, especially if you would like to see New Year's Eve. Ventricular tachycardia can cause the heart to beat uncontrollably or stop beating entirely. All of this from tiny little gates in cell membranes that decide which ion goes where and when. How cool is this?

WHAT DOES THIS HAVE TO DO WITH HCQ?

When drugs block the hERG (potassium) channel it can result in a condition called QT prolongation or Long *QT* syndrome (LQTS), which results in the heart beating quickly and erratically. This can be seen on an electrocardiogram (ECG).



Normal ECG ECG with prolonged QT interval

Sometimes QT elongation can cause a dangerous condition called "torsades de pointes" (French for “twisting of points”) where the heart’s two lower chambers (ventricles), beat faster than the upper chambers (atria). It is the mismatch of the timing of the lower and upper chamber that causes the problem.

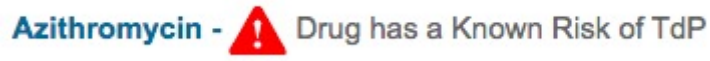
Source: Allphase Consulting [2]

RELEVANCE TO MEDICINE

There is a database called Credible Meds [3] that enables you to see which drugs cause prolonged QT intervals. The database ranks drugs for their ability to cause torsades de pointes (TdP).

Here's one:

And here's another:



So, what you've been hearing on the news should make sense. Hydroxychloroquine does have *some* cardiac risk because the molecule is known to block potassium channels. So does azithromycin. **(2)** When they are combined, the risk goes up; maybe by a lot.

POLITICIANS, PLEASE SHUT UP

Last I heard, voltage-gated ion channels do not register for primaries, and they vote only infrequently. We are talking about the binding of a drug (or any other molecule) to a channel whose job is to keep ions moving in and out of a cell in such a way that your heart beats properly. Not anything that should be part of a presidential campaign. It should be "torsades de pointes," not "talking de points." In other words, real science.

Such a thing still exists.

UPDATE 5/22

A large observational study [4] was just published in the Lancet. The authors claim that all combinations of hydroxychloroquine, chloroquine, and azithromycin resulted in more patient deaths than controls (no drugs given). Perhaps the most eye-opening result was the marked increased incidence of ventricular arrhythmias, which the authors associated with the excess deaths of the patients who took the malaria drugs. Here are the numbers:

Control (no drug): 0.3% incidence of ventricular arrhythmias

HCQ (alone): 6.1%

HCQ plus macrolide (azithromycin or clarrithomycin): 8.1%

Chloroquine (alone): 4.3%

Chloroquine plus macrolide: 6.5%

"Each of the drug regimens of chloroquine or hydroxychloroquine alone or in combination with a macrolide was associated with an increased hazard for clinically significant occurrence of ventricular arrhythmias and increased risk of in-hospital death with COVID-19."

M R Mehra, et. al., The Lancet, Online first. DOI:https://doi.org/10.1016/S0140-6736(20)31180-6 [5]

NOTES:

(1) This name isn't as stupid as it sounds. The hERG channel was discovered in fruit flies. The name comes from what was observed when they were anesthetized with ether. Their legs started shaking. OK, it's still pretty stupid-sounding.

(2) This does not mean that either HCQ or azithromycin will definitely cause heart problems. Most of the time they won't or they wouldn't be drugs. But, as with all other drugs, the relationship between risk and benefit is what matters. If the benefit of a drug is zero then taking it is insane.

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[2] http://allphasepharma.com/dir/2014/06/28/432/qt-prolongation-with-azithromycin-and-levofloxacin/
[3] https://crediblemeds.org/
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