What is the relationship between Digoxin and potassium?

Digoxin is a drug that is used to treat heart failure, a condition in which the heart muscle is weak and unable to pump blood effectively to the rest of the body. Digoxin can also be used to treat atrial fibrillation. It can be given to patients with heart failure in order to make more calcium available so that a stronger heart contraction can be generated. This ?uctuation in calcium levels can trigger a Delayed after-depolarization (DAD).

Delayed after-depolarisations (DAD)s is an example of triggered activity, a situation in which a set of cells generates an electrical signal through some action of the cell itself and not through repetition of a previous signal.

The key determinant of DADs is an elevation in free intracellular calcium (Ca2+) levels, which raise the cell's membrane potential to a threshold and, therefore, trigger an extra action potential.

An example of how a DAD can occur involves the drug digoxin acting on myocytes.

The relationship between digoxin and potassium.

To understand what is the relationship between digoxin and potassium when it comes to dysrhythmias its key to understand the mode of action of this drug: Digoxin.

Mode of action of digoxin

Digoxin works by two basic mechanisms of action and it is the mechanism at work in heart failure, involving **inhibition of the Na+/K+-ATPase pump**. The activity of the sodium-potassium ATPase pump is controlled by a phosphorylation event. If the pump is phosphorylated (i.e. has a phosphate group attached to it), then it has a high affinity for digoxin and vice versa.

The dose of digoxin can remain exactly the same but it will have a di?erent e?ect on the cell depending on whether or not the pump has been phosphorylated.

Since the process of dephosphorylation is controlled by the availability of potassium, a person who is hypokalaemic (having low potassium levels) can experience an apparent overdose of digoxin even if their treatment dose is within the therapeutic range because of the changed state of the sodium-potassium -ATPase pump.

If the dose of digoxin is high or the person has hypokalaemia, more of these pumps will be blocked. This means that sodium ion efflux (loss of sodium from the cell) is delayed, resulting in the local accumulation of sodium ions near the cell membrane. This excessive accumulation creates an apparent change to the gradient across the membrane, which will decrease the activity of the passive **Na+/Ca2+ exchange**r as this protein is dependent on a low intracellular Na+ concentration to function.

Reduced sodium-potassium exchanger activity will cause a delay in Ca2+ efflux (loss of calcium

ions) from the cell.

At standard doses of digoxin, or when potassium levels are normal, the accumulated calcium ion levels are small and are easily moved to the sarcoplasmic reticular (SR) store.

However, with digoxin levels high or potassium levels low, there is too much Ca2+ to be accommodated by the SR store, so sodium ions and calcium ions are retained in the cytoplasm. If the delay in the removal of these positive ions is sufficient, the membrane potential of the cell will be above the threshold when the **voltage-gated Na+ channels** return to rest, which will trigger an action potential.

In a person who either receives a too-high dose of digoxin or whose potassium levels are low (such as when treated with a potassium-wasting diuretic), blockage of the Na+/K+-ATPase pump by digoxin will be increased. This increase poses a risk of tachycardia due to DAD.

> If delayed after depolarization are due to elevated calcium levels, what does this have to do with the Na+/K+-ATPase pump?

The role of the Na+/K+-ATPase pump is to remove the sodium ions (Na+) that came into the cell during depolarization and retrieve the potassium ions (K+) lost during repolarization. Since this ion movement is contrary to the concentration gradient for each ion, it requires the use of energy, hence the ATPase function of the pump.

Therefore, when digoxin blocks the pump, it delays the removal of Na+ from inside the cell, allowing it to accumulate near the cell membrane. This results in an increase in the intracellular concentration of Na+, which stops the activity of the passive Na+/Ca2+ exchanger. This protein relies on the Na+ gradient across the membrane to bring a small quantity of Na+ into the cell in order to remove calcium (Ca2+) from the cell.

During the plateau phase of the action potential, a small amount of Ca2+ comes into the cell, triggering the release of the Ca2+ in the sarcoplasmic reticulum (SR) store.

At the end of the action potential, the majority of the Ca2+ returns to the SR store, but the remainder must be excreted from the cell. So, if the passive Na+/Ca2+ exchanger stops working, then free calcium is allowed to accumulate inside the cell.

As long as the cell remains in its refractory period, the retention of positive ions (Na+, Ca2+) inside the cell creates no problems. However, once the cell has returned to a resting state, it is ready for another action potential and, if the membrane potential (which is defined by the number of positive ions inside the cell), is at the threshold, then the cell will automatically initiate another action potential.

So, in the presence of either too high a dose of digoxin or when digoxin is used in a person with hypokalaemia, the intracellular concentrations of Na+ and Ca2+ will be potentially too high, due to the failure of the pump and the exchanger. If these concentrations are sufficient to reach a threshold, the cell will fire, and so will its neighbors, resulting in an additional heartbeat.