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It's time to make melatonin a useful tool in improving cardiac rhythmicity

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Melatonin has a profound effect on the pacemaker of the central mechanism of a heart.[1–3] That this heart is in a fly should not affect the importance of this fact. *Drosophila melanogaster* has done yeoman service across biology beginning with providing the foundation of modern genetics.[4,5] Multiple Nobel prizes, the most recent in 2017, have gone to those working with the fly.[5] This fly work includes cardiology. The fly heart has been studied extensively.[6–10] Its physiology has been described in detail and this includes an understanding of basic hormonal control.[11,12] The sarcolemmal pacemaker's central ion channels are well established, and the physiology and components of the companion cytosolic pacemaker have also been studied in detail.[11–18] The utility of the fly genome in the study of the mammalian heart has been clearly proven. Long QT syndrome, a congenital problem in which individuals suffer a delay in cardiac repolarization,[19–21] has been found to be a result of a mutation in a gene originally found in the fly.[22–25] The human Ether a go Related Gene, or hERG is a homolog of the fly gene *seizure* and cDNA from this gene was used to locate its human relative.[22] There have been over 1600 human disease genes uncovered to date and nearly three quarters of these have *Drosophila* homologs. About 500 are highly conserved and known to be functionally equivalent in both organisms.[26] With this mind, cardiologists might well look to the fly for answers to basic questions about underlying heart physiology, genetics, and pathology.

Melatonin makes the fly heartbeat extremely regular.[1–3] It cannot be emphasized too strongly that the alteration in heartbeat we observe is unprecedented. We showed this is not an artifact of an increase in rate.[1] Melatonin is commonly used in humans to prevent damage by reactive oxygen species (ROS) during reperfusion after myocardial infarction.[27] Reports of increased heartbeat regularity attribute this to the antioxidant effects.[27–31] However, this was shown not to be the case in the fly; ascorbic acid has no such effect in *Drosophila*.[1] It is important to note here that the profound change in the signal to noise ratio in the fly work is against a background of a fairly irregular heartbeat in the normal fly.[1–3] Mammalian hearts are also not particularly regular under normal conditions, to the point that there has been considerable work done to find out if this is a result of the underlying oscillator being fundamentally chaotic.[32–34] In humans, an abnormally regular heartbeat can be a sign of congestive heart failure.[32–34]

One crucial observation from these studies is that melatonin can yield normal wild–type heart function in flies carrying a mutation in one of the genes encoding a central ion channel in the sarcolemal pacemaker, *slowpoke*, which normally shows a weak, highly erratic heartbeat.[14] The beating observed after melatonin application is equal to the extremely abnormal high regularity seen in wild–type. This is, by itself, a provocative finding. It would be comparable to a car being made to run normally with an engine which has broken a

camshaft. A possible explanation is at hand. Considerable evidence has accumulated that there is a second cardiac pacemaker in the cytosol termed the LCR, for Local Calcium Release.[35–39] Evidence for such an oscillator is strong. One compelling observation is that pacemaking can continue in a vertebrate heart cell when the plasma membrane of the cell is voltage clamped![35] This oscillator depends on Calcium currents passing through the membrane of the sarcoplasmic reticulum.[35–39] There are two central ion channels: one is the ryanodine receptor allowing efflux and the other is the Sarcoplasmic/Endoplasmic Calcium ATPase (SERCA) effecting reuptake.[40–42] Mutations in the genes encoding these channels affect heart function considerably[40–42] and melatonin is relatively ineffective in ameliorating the effects.[3] An immediate hypothesis is that melatonin is fundamentally affecting the communication between these two pacemakers. If the sarcolemmal oscillator fails, responsibility would shift entirely to the LCR system. A switch to the LCR oscillator would also explain the wild–type results.[1–3]

It is of importance to learn how melatonin works. Two possibilities present themselves. The effect could be directly on the pacemaker through interactions with the ion channels comprising the oscillator. A second control pathway possibility would be through binding with a receptor. The latter is initially favored by the kinetics of the alteration. We observed that the switch between normal mode and hyper regularity occurs sharply, literally from one beat to the next after an interval post injection.[1] With this in mind, we tested melatonin receptor agonists and antagonists with positive results. Luzindole is a melatonin receptor antagonist, and it is effective in interdicting melatonin's action. In contrast**,** 2-[^{125}I] iodomelatonin, a melatonin agonist, is even more effective in increasing the rhythmicity than melatonin.[1] The next step was to identify the receptor. We used RNAi knockout techniques to probe likely orphan G Protein Coupled Receptor (GPCR) genes for a candidate. Knocking out the function of the CG4313 orphan completely eliminated the melatonin response.[1] This finding makes it almost certain that the mechanism is receptor mediated.

The flies have done their job. There is ample reason to hypothesize that given the similarities between the systems, these findings could be extended to the mammalian heart. The reported examples of increased regularity in hearts given melatonin to preclude reperfusion damage after infarct are strong evidence this is the case, especially in light of our finding that the antioxidant ascorbic acid has no effect on rhythmicity.[1] The basic work needs to be done, and translational work would not be far behind.

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Conflicts of Interest

The author declares that there are no conflicts of interest.

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