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RESEARCH NEWS

Catecholamines help snakes have a change of heart

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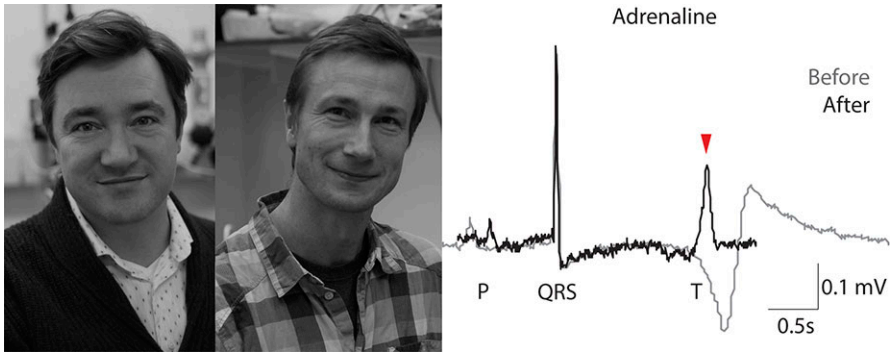
***JGP* study on python snakes reveals that the regulation of ventricular repolarization by the sympathetic nervous system is evolutionarily conserved.**

The T-wave of an electrocardiogram (ECG) arises from local differences in ventricular repolarization and represents a vulnerable period for the generation of arrythmias when some, but not all, of the myocardium is still refractory and unable to generate a new action potential. In mammals, ventricular repolarization is regulated by catecholamines released by the autonomic nervous system. In this issue of *JGP*, Boukens et al. show that this mode of regulation is conserved in the ball python, *Python regius* (1).

Working together at Amsterdam UMC, Bas Boukens and Bjarke Jensen are interested in the electrophysiological adaptations that have occurred during cardiac evolution. Cold-blooded reptiles have a much longer ventricular repolarization phase than warm-blooded mammals, even at 37°C (2). Moreover, the T-wave is typically negative in reptiles, whereas in mammals it is usually positive. Anecdotal observations, however, suggest that, in some reptiles, the T-wave can invert and become positive at higher body temperatures (3, 4). "We were curious about what might underlie these observations," Jensen says.

The researchers therefore recorded ECGs in living ball pythons as their body temperatures were increased (1). The ball python's heart is unique in having functionally distinct ventricles, with a high-pressure left side and a low-pressure right side, even though, as in other snakes, the two sides are not anatomically separated. Though results varied across individual pythons and ECG leads, raising body temperature from 25 to 35°C caused an inversion of the snakes' T-wave, reflecting temperature-dependent changes in the pattern of ventricular repolarization.



Bas Boukens (left), Bjarke Jensen (center), and colleagues reveal that, similar to mammals, catecholamines released by the autonomic nervous system regulate ventricular repolarization in ball pythons. An ECG (right) shows that, by altering the pattern of ventricular repolarization, adrenaline treatment causes an inversion of the T-wave (red arrowhead). A similar phenomenon is observed in snakes undergoing a rise in body temperature, when autonomic tone increases.

In 1880, Burdon-Sanderson and Page (5) showed in their classic experiments that local differences in temperature change T-wave polarity in the ectothermic heart, presumably due to a direct effect of temperature on the activity of cardiac ion channels. However, when Boukens et al. recorded an ECG from a decapitated python, they found that raising temperature did not cause T-wave inversion (1). "So, we realized that it might not be a direct effect of temperature but might involve another factor, namely catecholamines released by the autonomic nervous system," says Boukens. Autonomic activity increases at higher temperatures, but the ability of catecholamines to modulate ventricular repolarization would be blunted in decapitated snakes lacking a functional nervous system.

Sure enough, the researchers found that stimulating the β-adrenergic receptor induced T-wave inversion in pythons maintained at a stable temperature. In contrast, the β blocker propranolol largely prevented higher temperatures from inducing T-wave inversion.

Thus, similar to mammals, catecholamines regulate ventricular repolarization in ball pythons, and the increase in autonomic tone at higher temperatures alters the pattern of repolarization and changes T-wave shape. "The T-wave inversion suggests that certain regions of the python heart respond more strongly to adrenergic stimulation than other regions," Boukens says.

To test this idea, the researchers performed RNA sequencing of tissue samples taken from different regions of the python heart. "Catecholamine-associated genes exhibited differential expression between the left and right sides of the ventricle, consistent with the repolarization of these regions

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being differentially modulated by adrenergic signaling," says Jensen.

This may provide some sort of advantage to pythons as their body temperature rises, though the resulting changes in repolarization pattern could also leave them vulnerable to developing arrythmias. Boukens and Jensen are now extending their studies to a different branch of the evolutionary tree, examining repolarization and arrhythmogenesis in zebra finches (6).

References

1. Boukens, B.J.D., et al. 2021. *J. Gen. Physiol.* 154: e202012761. https://doi.org/10.1085/jgp.202012761
2. Boukens, B.J.D., et al. 2019. *Prog. Biophys. Mol. Biol.* 144:16–29. https://doi.org/10.1016/j.pbiomolbio.2018.08.005
3. Mullen, R.K. 1967. *Physiol. Zool.* 40:114–126. https://doi.org/10.1086/physzool.40.2.30152446
4. Valentinuzzi, M.E., et al. 1969. *J. Electrocardiol.* 2: 245–252. https://doi.org/10.1016/S0022-0736(69)80084-1
5. Burdon-Sanderson, J., and F.J.M. Page. 1880. *J. Physiol.* 2:384–435. https://doi.org/10.1113/jphysiol.1880.sp000070
6. Offerhaus, J.A., et al. 2021. *Physiol. Rep.* 9:e14775. https://doi.org/10.14814/phy2.14775