Measuring Physiological Response of Bisphenol-A on Cardiac Excitation-Contraction Coupling

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Introduction

Bisphenol-A (BPA) is an endocrine-disrupting compound (EDC) commonly found in consumer plastics. Environmental exposure varies between 1–100 nM, while clinical and industrial exposure can reach 10 uM. The aim of this project is to determine the effects of BPA on cardiac mechanical function and calcium handling.

Objectives

To detect the effects of BPA exposure (15 min) on left-ventricular developed pressure (LVdP) and contractility (dP/dt). To monitor changes in epicardial calcium handling with increasing BPA doses and pacing frequencies.

Methods

We aimed to test the direct effects of BPA on cardiac function using a Langendorff-perfusion model. Excised female rat hearts were treated with 1 nM-10 uM BPA and the resulting effects on cardiac mechanical function and calcium handling were monitored. For calcium imaging, excised hearts were treated with Blebbistatin to arrest mechanical function, and then stained with Rhod-2, a calcium indicator dye. Epicardial calcium transients were recorded using an Andor CCD camera equipped with wavelength specific filters (570+/- 30 nm), and an LED spotlight (535 nm) was used for dye excitation. Calcium transients were initiated at various pacing frequencies (5Hz, 6.6Hz, and 9Hz). To assess the effect of BPA on the mechanical function of the heart, a latex balloon was inserted into the left-ventricle to quantitate left-ventricular developed pressure (LVDP) and maximum contractility.

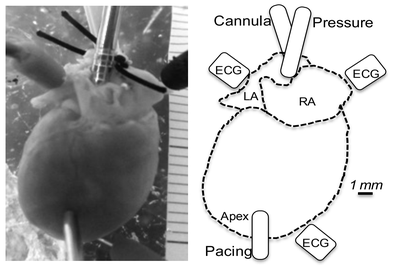

Fig. 1. Excised whole heart on Langendorff-perfusion model

Results

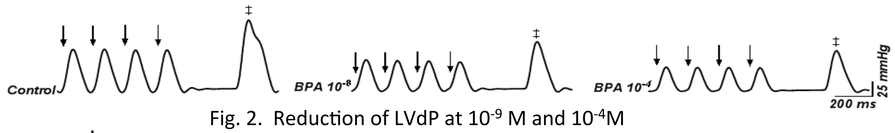

Fig. 2. Reduction of LVdP at 10^{-9} M and 10^{-4}M

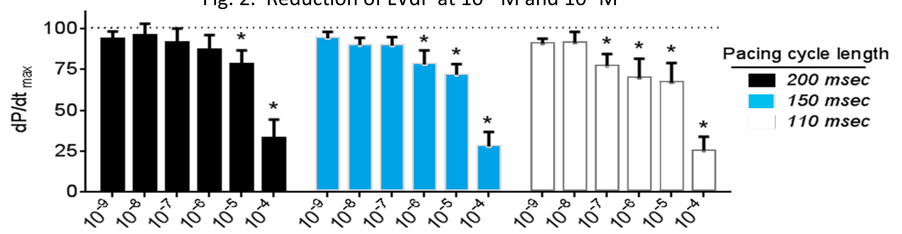

Fig. 3. BPA dose-response effect on max dP/dt

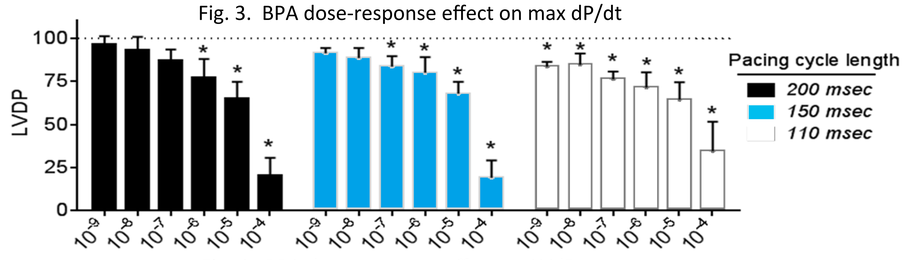

Fig. 4. BPA dose-response effect on LVdP

Discussions

Previous studies have shown that BPA exposure can prolong ECG PR segment, increase action potential duration, and decrease conduction velocity in excised female rat hearts [2]. Since alterations in conduction velocity can affect ventricular pressure [3], we aimed to investigate the effect of BPA exposure on cardiac mechanical function. We hypothesized that a decrease in cardiac left ventricular pressure, due to delayed conduction velocity, could also result in decreased contractility (rate measurement of LVdP).

Analysis of Ca^{+2} transients indicated that, at high pacing frequencies, BPA exposure hinders the frequency potentiation response of cardiac tissue. Frequency potentiation is an adaptive mechanism whereby cardiac contractility increases at fast heart rates to maintain cardiac output. Cardiac contractility is dependent upon the concentration of intracellular Ca^{+2} ions that are released by the sarcoplasmic reticulum (SR) with each round of contraction. Alterations in calcium handling and contractility can impact the heart's ability to adapt to high heart rates under exercise or stress conditions.

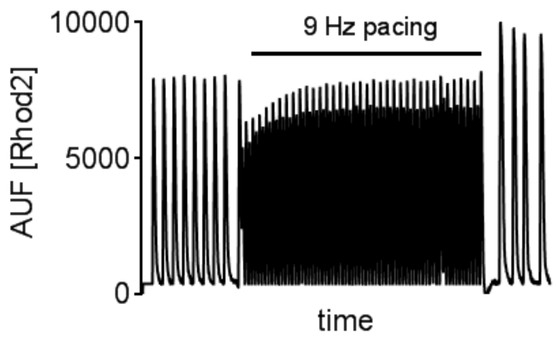

Fig. 5. Calcium Transients at 9Hz (110 ms) pacing frequency

Conclusion

Previously, it was shown that BPA significantly decreases cardiac electrical conduction [2]. Current results indicate that BPA significantly decreases cardiac mechanical function, specifically LVdP and dP/dt. A decrease in the synchronization of the electrical conduction of the whole heart can initiate negative repercussions for cardiac output. Decreased conduction velocity can slow the synchronization of cardiac contraction, thereby reducing LVdP and dP/dt. These results are clinically relevant, particularly in populations that with pre-existing heart conditions since continued exposure to BPA could further reduce overall cardiac function. It is concluded that alterations to cardiac mechanical function and calcium handling are a sensitive parameter for assessing BPA cardiac toxicity. The findings indicate that further studies are necessary to clarify the complete extent through which BPA affects cardiovascular function.

References

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