Supplemental Material

Bisphenol A Exposure and Cardiac Electrical Conduction in Excised Rat Hearts

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Table of Contents

Figure S1 Page 2

Table S1 Page 4–5

References Page 6–7

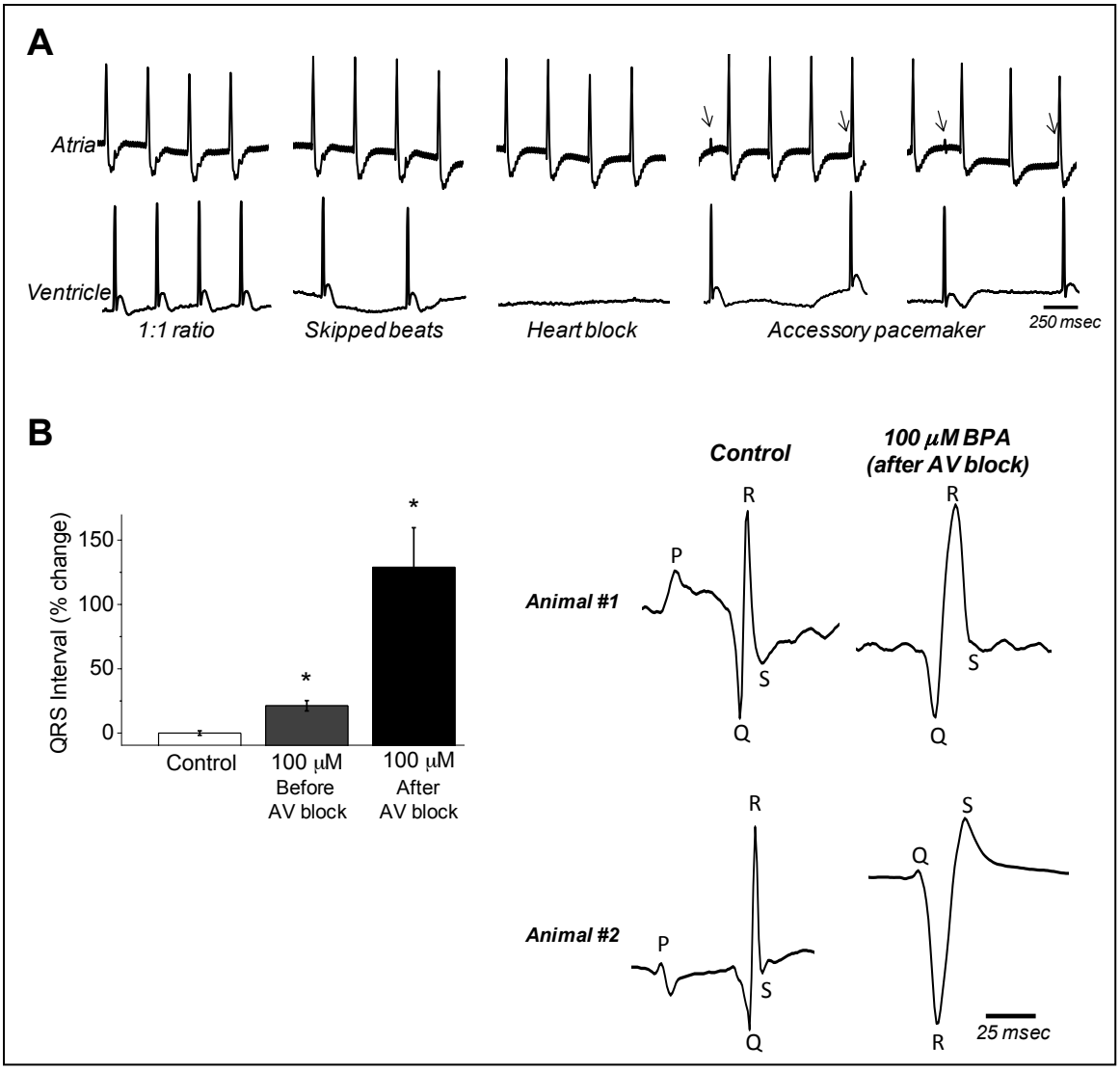

Figure S1. Exposure to high concentrations of BPA results in 3rd degree AV block. **A.** Time course of AV block after exposure to 100 μM BPA (atrial and ventricular signals are shown). AV conduction ratio progressed from 1:1 to 2:1 (2nd degree AV block). Across all studies, 2nd degree AV block occurred within 3.6 ± 2.4 minutes after raising BPA concentration to 100 μM. After this, hearts quickly progressed to complete failure of AV conduction (3rd degree AV block). Across all studies, 3rd degree AV block occurred within 4.3 ± 2.6 min after raising BPA to 100 μM. At this point, there was a short pause where no electrical activity was measured with the apical recording electrode. Ventricular activation then resumed and was driven by an

accessory pacemaker that activated the ventricles independently of the atrium (denoted by arrows [Zipes and Jalife, 2009]). **B.** Left: 100 μM BPA increases the QRS interval ($n \geq 3$, $^{*}p < 0.05$). Right: ECG signals show widening of the QRS interval and changes in QRS morphology.

Table S1. Experimental studies that investigate possible mechanisms underlying BPA's impairment of conduction velocity (illustrated in Figure 4).

Possible mechanisms	Source	Chemical	Cell type	Experimental outcome
1	O'Reilly et al. 2012	Bisphenol A	HEK293 ($Nav_{1.5}$ transfected)	BPA binds and blocks voltage-gated Na^+ channel. Effect at 1 μM BPA, acute treatment (4 min)
2	Asano et al. 2010	Bisphenol A	Coronary muscle neurons	BPA binds and activates Maxi-K^+ channels. Effect at 10 μM BPA, acute treatment (< 1 min, reversible)
3	Liu et al. 2010	Raloxifene	Ventricular cardiomyocytes	Raloxifene (ER agonist) decreased Na^+ current
3	Wang et al. 2013	Bisphenol A	Dorasal root ganglion neurons	BPA inhibits tetrodotoxin-sensitive and resistant Na^+ current. BPA's effect is blocked by PKC and PKA inhibitors. IC50 = 11.6 μM BPA (5 min), partially reversible with washout.
4	Druzin et al. 2011	Estradiol	Medial preoptic neurons	17-β-estradiol (ER agonist) binds to open K^+ channels to reduce voltage-gated K^+ current
4	Moller and Netzer 2006	Estradiol	CHO cells	17-β-estradiol inhibited voltage-gated K^+ channels
4	Kurokawa et al. 2008	Estradiol	Ventricular cardiomyocytes, CHO cells (hERG transfected), Guinea pig hearts	17-β-estradiol suppressed K^+ current (hERG channel gating), results in QT prolongation
4	Tanabe et al. 1999	Estradiol	Ventricular cardiomyocytes	17-β-estradiol prolonged APD and repolarization time mainly by inhibiting K^+ current
4	Berger et al. 1997	Estradiol	Ventricular cardiomyocytes	17-β-estradiol reduced K^+ current and prolonged APD
4	Nakajima et al. 1999	Estradiol	Atrial cardiomyocytes	17-β-estradiol inhibited K^+ current
5	Lee et al. 2002	Estradiol	Dorsal root ganglion neurons	17-b-estradiol inhibits L-type Ca^{2+} current via activation of pertussis toxin-sensitive G-proteins
5	Tanabe et al. 1999	Estradiol	Ventricular cardiomyocytes	17-β-estradiol reduced L-type Ca^{2+} current, prolonged APD and repolarization time
5	Berger et al. 1997	Estradiol	Ventricular cardiomyocytes	17-β-estradiol reduced L-type Ca^{2+} current
5	Nakajima et al. 1999	Estradiol	Atrial cardiomyocytes	17-β-estradiol inhibited cAMP-enhanced L-type Ca^{2+} current, effect was blocked by cGMP or L-NAME (NOS inhibitor) pretreatment

Possible mechanisms	Source	Chemical	Cell type	Experimental outcome
5	Jiang et al. 1992	Estradiol	Ventricular cardiomyocyte	17-β-estradiol decreased peak inward Ca^{2+} current
5	Meyer et al. 1998	Estradiol	Ventricular cardiomyocytes	17-β-estradiol inhibited L-type Ca^{2+} current
6	Jiang et al. 1992	Estradiol	Ventricular cardiomyocyte	17-β-estradiol has a negative inotropic effect, decreases myocyte cell shortening
6	Pant et al. 2011	Bisphenol A	Isolated atrial preparations	BPA decreased atrial contractility, effect was blocked by pretreatment with L-NAME (NOS inhibitor) or methylene blue (guanylyl cyclase inhibitor). Effect at 0.1 μM BPA (10 min)
6	Belcher et al. 2011	Bisphenol A	Ventricular cardiomyocytes	BPA reduced contractility via estrogen receptor beta signaling, pretreatment with L-NAME (NOS inhibitor) did not alter BPA's effects. Effect at 10^{-12}M BPA, acute treatment (2-7min)
6	Liew et al. 2004	Raloxifene	Ventricular cardiomyocytes	Raloxifene decreased cell shortening, decreased Ca^{2+} transient amplitude, and decreased L-type Ca^{2+} current. Raloxifene effects inhibited by pretreatment with estrogen receptor antagonist

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