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The Role of Endothelin-1 in Cardiac Hypertrophy Observed in Aryl Hydrocarbon Receptor (AhR) Null Mice.

OVERVIEW

The Aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor known to mediate the toxicity of environmental pollutants such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), polychlorinated biphenyls and polycyclic hydrocarbons. The role of the AhR in physiological homeostasis is still uncertain, however functional inactivation of the AhR (as seen in AhR null mice) results in profound effects on the cardiovascular system, characterized by progressive cardiac hypertrophy. By five months of age, AhR null mice develop cardiac hypertrophy, with significant increases in left ventricular mass and expression of cardiac hypertrophy marker genes β-myosin heavy (β-MHC) chain, and atrial naturetic factor (ANF). However, the mechanisms underlying the development of cardiac hypertrophy in these mice have not yet been elucidated. Because of the marked effect of left ventricular (LV) mass on cardiovascular morbidity, it is important to identify the factors that initiate left ventricular hypertrophy (LVH).

There are several factors that are associated with the clinical onset of LV growth, one of is endothelin-1 (ET-1). ET-1 is the most potent vasoconstrictor and a direct acting mitogen that has been associated with cardiomyocyte hypertrophy. We have previously reported AhR null mice exhibit cardiac hypertrophy associated with elevated ET-1. Thus, the purpose of this research is to elucidate the role of ET-1 in the progression of cardiac hypertrophy in AhR null mice.

RESEARCH APPROACH

To better understand the role of ET-1 in cardiac hypertrophy, we tested the hypothesis that **cardiac hypertrophy in AhR null mice results from an increase in ET-1 expression and downstream pathways regulated through the ET_A receptor.** To do this, the following set of experiments was conducted:

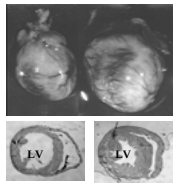
1. Determine the age of onset and rate of progression of cardiac hypertrophy by measuring tissue weights and expression of genes associated with cardiac hypertrophy (β-MHC and ANF).

2. Measure ET-1 levels in tissue and plasma at different age time points.

3. Attempt to prevent onset and/or progression of cardiac hypertrophy by chronically treating AhR null mice with BQ-123, and ET_A-receptor antagonist (blocks effects of ET-1 on heart) from age 2 through 4 months old.

RESULTS

AhR null mice develop age-progressive cardiac hypertrophy.

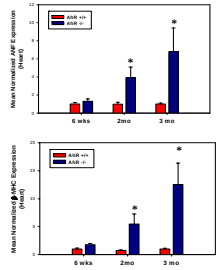


AhR Wildtype AhR Null

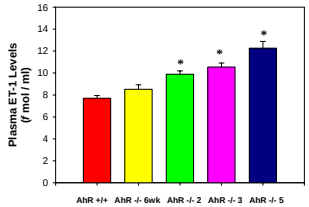
	Heart weight (g)	Body Weight (g)	HW / BW Ratio (x100 g)
AhR Wildtype:			
6 wks	0.111 ± 0.003	22.2 ± 0.4	0.499 ± 0.009
2 mo	0.125 ± 0.002	27.8 ± 0.9	0.477 ± 0.008
3 mo	0.142 ± 0.003	31.1 ±0.7	0.456 ± 0.005
AhR Null:			
6 wks	0.113 ± 0.003	20.8 ±0.5	0.545 ± 0.007*
2 mo	0.159 ± 0.005†	27.5 ± 0.7	0.579 ± 0.024†
3 mo	0.160 ± 0.004‡	30.0 ± 0.9	0.540 ± 0.013‡

* p < 0.050 compared to AhR wildtype 6 wks
† p < 0.050 compared to AhR wildtype 2 mo
‡ p < 0.050 compared to AhR wildtype 3 mo

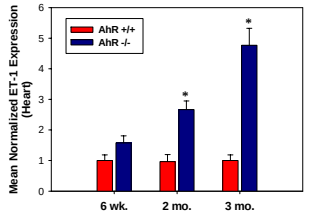
AhR null mice show an age-progressive increase in levels of cardiac hypertrophy marker genes.



AhR null mice exhibit significantly elevated plasma ET-1 levels, which increase with age.



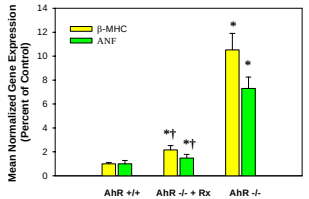
AhR null mice display increased cardiac ET-1 mRNA levels, compared to AhR wildtype mice.



* p < 0.050 compared to AhR Wildtype
† p < 0.050 compared to AhR Null

BQ-123-Treatment (+Rx) results in significant Decrease in heart weight, and expression of cardiac hypertrophy marker genes.

	Heart Weight (g)	Body Weight (g)	HW / BW Ratio (x100 g)
AhR Wildtype	0.148 ± 0.006	31.2 ± 0.8	0.478 ± 0.009
AhR Wildtype + Rx	0.150 ± 0.002	31.7 ± 0.5	0.475 ± 0.007
AhR Null	0.179 ± 0.006*	32.6 ± 1.3	0.552 ± 0.012*
AhR Null + Rx	0.162 ± 0.005†	33.0 ± 1.0	0.492 ± 0.007†



SIGNIFICANCE / IMPACT

The AhR is known to mediate the toxicity of several environmental pollutants, however the regulation and function of the AhR are still largely unknown. Exposure to TCDD has been correlated to an increased risk of cardiovascular events such as ischemia, but the mechanisms by which TCDD exposure results in such clinical events remain uncertain. Through investigation of the functions of the AhR, we can begin to understand how activation of the AhR results in pathologies seen as a result of exposure to such pollutants. Additionally, potential polymorphisms in AhR, or the proteins which regulate AhR function, could represent risk factors associated with human hypertension and hypertrophic heart disease. Thus, such research will likely lead to potential targets for drug therapies to prevent progression of cardiovascular disease states associated with exposure to certain environmental pollutants.

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