Crosstalk between aryl hydrocarbon receptor and Wnt/β-catenin signaling pathway: possible culprit of di (2-ethylhexyl) phthalate-mediated cardiotoxicity in zebrafish larvae

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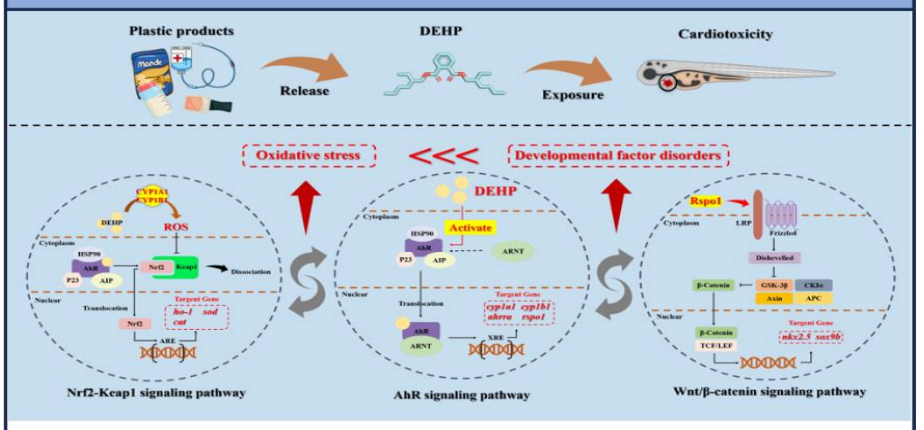
Abstract & Highlights



- ✓ DEHP mediated cardiac developmental defects by activation of the AhR signaling pathway.
- ✓ DEHP-mediated oxidative stress partially attributed to its AhR agonistic activity.
- ✓ DEHP-mediated cardiac rate abnormalities are independent of its AhR agonistic activity.

Result

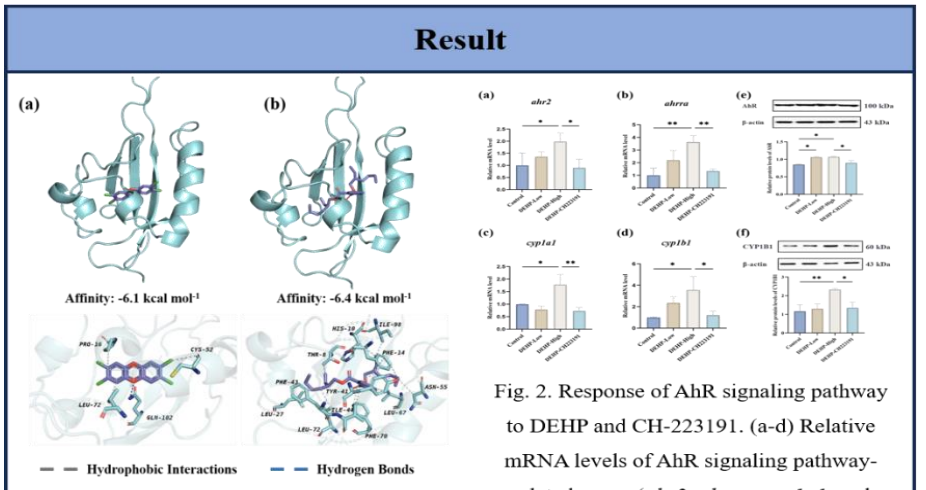


Fig. 1. Detailed docking results of TCDD (a) and DEHP (b) with LSD of AhR.

Fig. 2. Response of AhR signaling pathway to DEHP and CH-223191. (a-d) Relative mRNA levels of AhR signaling pathway-related genes (*ahr2*, *ahrra*, *cyp1a1*, and *cyp1b1*). (e and f) Protein levels of AhR and CYP1B1.

Result

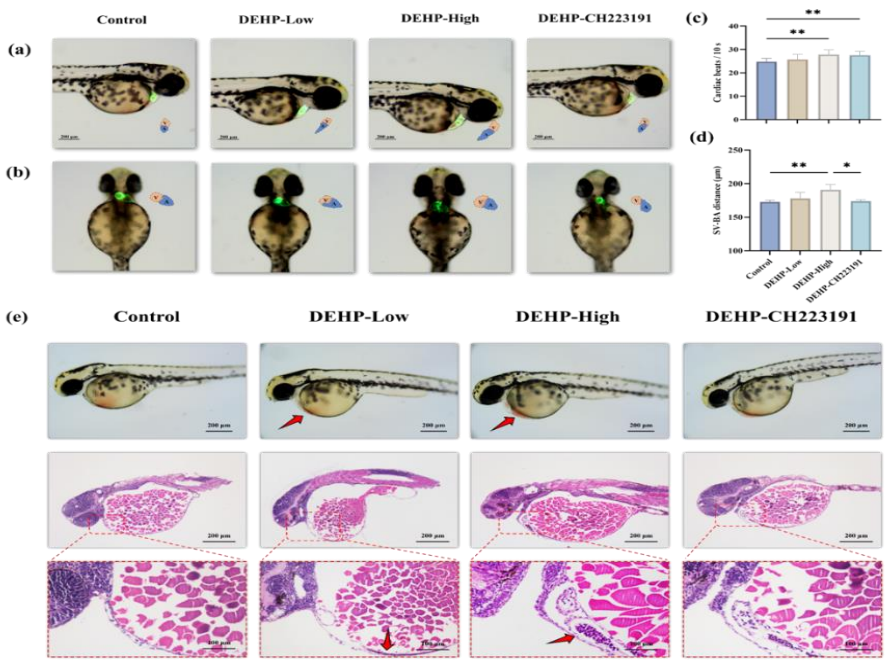


Fig. 3. DEHP-mediated phenotypic and histopathologic changes in the zebrafish cardiac. Side view (a) and top view (b) of transgenic zebrafish (*cmlc2: eGFP*), (c) cardiac rate, (d) SV-BA distance, (e) histopathologic changes. Red arrow: congestion..

Result

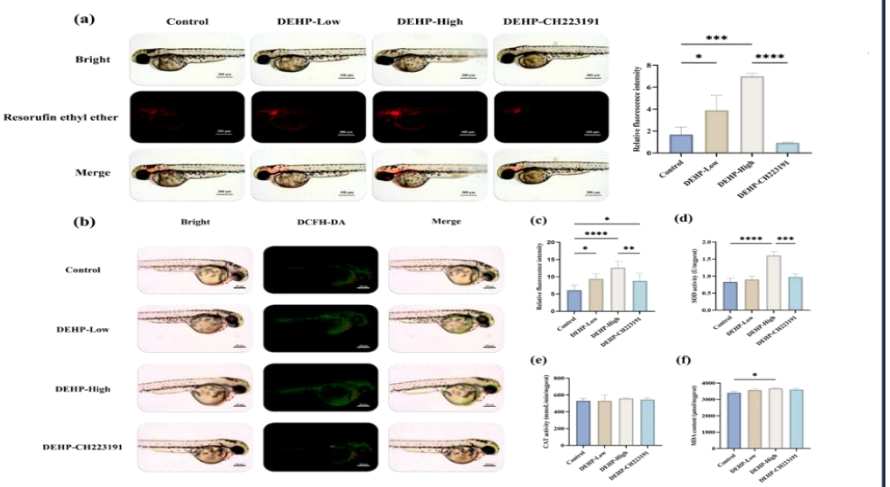
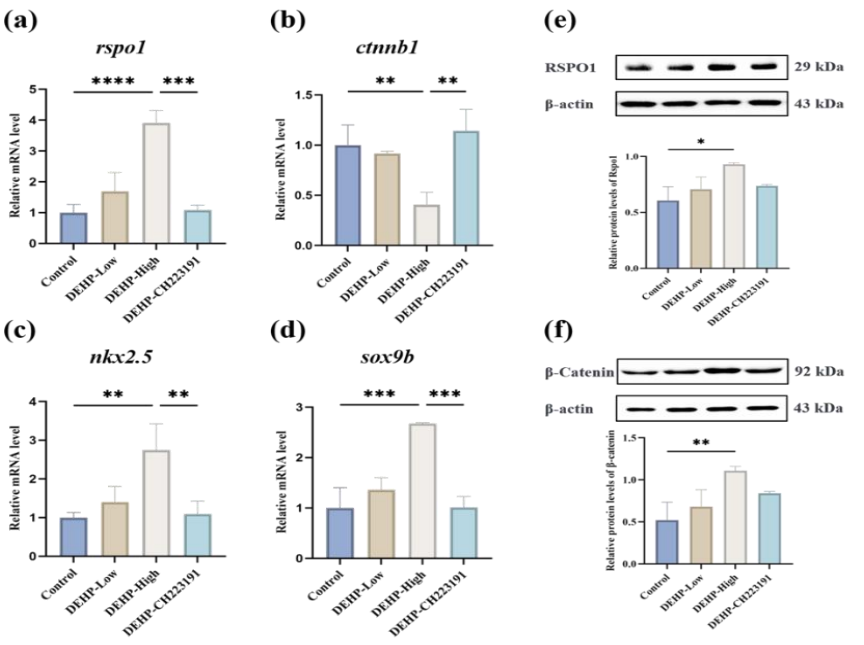


Fig. 4. DEHP-mediated AhR activation and oxidative stress in zebrafish larvae. Representative images and quantitative results of CYP1A1 activity (a) and ROS level (b and c). SOD, CAT activity (d and e) and MDA levels (f).

Result



Response of Wnt/β-catenin signaling pathway to DEHP and CH-223191. (a-d) Relative mRNA levels of AhR signaling pathway-related genes (*rspo1*, *ctnnb1*, *nkx2.5*, and *sox9b*). (e and f) Protein levels of RSPO1 and β-Catenin.

Conclusion

In conclusion, this work confirms that DEHP mediates early cardiac developmental and functional defects in zebrafish. Among them, the cardiac oxidative stress mediated by DEHP is partly attributed to its activating effect on AhR. Moreover, the crosstalk between AhR and Wnt/β-catenin signaling pathway seems to be one of the major means by which DEHP mediates cardiac developmental defects. It is noteworthy that AhR seems to be only involved in DEHP-mediated cardiac developmental defects rather than cardiac rate imbalance. Finally, this study firstly confirmed the activation of AhR in zebrafish by DEHP, and the above results will provide novel idea for scholars conducting ecological risk assessment or toxicological studies of DEHP in the future.