Biopolymers Research

Gomez, Biopolymers Res 2023, 7:6

Mini Review Open Access

Interaction between the Wnt/ β -catenin Signaling System and the Aryl Hydrocarbon Receptor: Potential Cause of Di(2-ethylhexyl)phthalate-Induced Cardiotoxicity in Zebrafish Larvae

Joseph Gomez*

Department of Microbiology, School of Life Sciences, Somalia

Abstract

Zebrafish have been shown to experience cardiotoxicity when exposed to typical plasticizer di (2-ethylhexyl) phthalate (DEHP), yet the possible chemical pathways underlying this have not yet been completely understood. It has been shown that DEHP activates the important protein AhR, which causes developmental defects in other species. However, it is unknown if AhR signaling pathway also plays a role in DEHP-mediated cardiac developmental toxicity in zebrafish. Initially, it was suggested by molecular docking simulations that DEHP might have AhR agonistic activity. This paper examined the alterations in cardiac-related indices at the individual, protein, and gene levels in zebrafish stressed by DEHP in order to further support this hypothesis. The findings demonstrated that DEHP caused oxidative stress, elevated CYP1A1 activity, cardiac developmental abnormalities, and notable alterations in the expression levels of AhR, Wnt/β-catenin, and Nrf2-Keap1 signaling pathway proteins and genes.

Keywords: 2-Ethylhexyl phthalate; AhR signalling; Zebrafish larvae; Cardiotoxicity; DEHP

Introduction

Tens of thousands of food products had grossly excessive levels (>1 ppm) of the endocrine disruptor plasticizer di (2-ethylhexyl) phthalate (DEHP), which Taiwan's Food and Drug Administration (TFDA) and Department of Health (DOH) accidentally discovered in 2011; some of the contaminated products had already been sold to over 20 countries. In subsequent epidemiologic investigations of children who ingested DEHP-contaminated foods, DEHP intake was significantly associated with glomerular and thyroid damage in children [1,2].

Methodology

While the National Toxicology Program Human Reproductive Risk Assessment Center detailed the possible reproductive and developmental toxicity of DEHP as early as 2002, and the Environmental Protection Agency of the United States and the European Union have designated it as a priority contaminant for control, a recent environmental finding shows that peak concentrations of DEHP in South Florida's drinking and surface waters still reach 1.562 and 3.698 μg L^{-1}. More concerningly, DEHP or its metabolite has been found worldwide in human blood, milk, and urine in addition to environmental media.

The average concentration of MEHP was found to be 1.51 μg L^{-1} in 139 serum samples from pregnant women collected in Zhejiang, China, in addition to European populations. Furthermore, DEHP metabolites constituted the majority of the 389 μg L^{-1} median total concentration of phthalate metabolites found in the urine of workers (n = 117) in an electronics factory in Tianjin, China. These days, an increasing amount of data indicates that DEHP is frequently found in humans, which surely represents a major risk to human health [3].

The average concentration of MEHP was found to be 1.51 μg L^{-1} in 139 serum samples from pregnant women collected in Zhejiang, China, in addition to European populations (Wang et al., 2023a). Furthermore, DEHP metabolites constituted the majority of the 389 μg L^{-1} median total concentration of phthalate metabolites found in the urine of workers (n=117) in an electronics factory in Tianjin, China. These days, an increasing amount of data indicates that DEHP is frequently found in humans, which surely represents a major risk to human health [4,5].

Malformation rates (pericardial edema, yolk sac edema, and craniofacial cartilage malformations) were found to be significantly higher in the DEHP-exposed group in a study involving zebrafish embryos. Subsequent research revealed that the mechanisms of DEHP-induced neurodevelopmental toxicity included oxidative stress, apoptosis, and disruption of dopamine signaling. More concerningly, there seems to be a possible link between children recovering in intensive care units' cognitive deficits, developmental delays, and physical deterioration and their extended use of DEHP-containing medical products during treatment (Vanhorebeek et al., 2022). The results above clearly show that developmental toxicity caused by DEHP should also not be disregarded. While there is no denying that DHEP has detrimental effects on the heart system, the underlying mechanisms are still unclear [6,7].

As common cytoplasmic proteins found in both adult and embryonic organisms, aryl hydrocarbon receptors (AhR) are known to be necessary ligands for the toxic effects of polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and tetrachlorodibenzo-p-dioxin (TCDD). By identifying and binding to xenobiotic response elements on DNA, the ligand-activated AhR translocates to the nucleus and forms a dimeric complex with aryl hydrocarbon receptor nuclear translocator (ARNT), which further regulates the expression of genes related to the cytochrome P450 (CYP450) family. As studies went on, it was determined that aberrant activation of the AhR signaling pathway, which is closely linked to the occurrence of oxidative stress, is also connected to early developmental abnormalities in the embryo. Reactive oxygen species (ROS) build

***Corresponding author:** Joseph Gomez, Department of Microbiology, School of Life Sciences, Somalia, Haiti, E-mail: joseph39@hotmail.com

Received: 03-Nov-2023, Manuscript No: bsh-23-120362; **Editor assigned:** 06-Nov-2023, Pre-QC No: bsh-23-120362 (PQ); **Reviewed:** 20-Nov-2023, QC No: bsh-23-120362; **Revised:** 22-Nov-2023, Manuscript No: bsh-23-120362 (R); **Published:** 29-Nov-2023, DOI: 10.4172/bsh.1000184

Citation: Gomez J (2023) Interaction between the Wnt/β-catenin Signaling System and the Aryl Hydrocarbon Receptor: Potential Cause of Di(2-ethylhexyl)phthalate-Induced Cardiotoxicity in Zebrafish Larvae. Biopolymers Res 7: 184.

up excessively when CYP450-related genes regulated by the AhR signaling pathway have their transcript levels upregulated. However, by encouraging Nrf2 translocation into the nucleus, activated AhR is also thought to activate the antioxidant response mediated by the Nrf2-Keap1 signaling pathway [8-10].

Results

In actuality, an organism's early stages of development are tightly controlled. Anomalous expression of signaling pathways linked to development can cause aberrant development and even the death of the organism, in addition to detrimental effects like oxidative stress. The Wnt/β-catenin signaling pathway is a significant pathway that plays a vital role in controlling the differentiation of progenitor cells and the formation of organs. According to the studies that are currently available, when AhR agonists mediated the abnormal activation of the AhR signaling pathway, which is linked to the crosstalk between the two pathways mentioned above, the expression levels of genes or proteins related to the Wnt/β-catenin signaling pathway were also disrupted.

Discussion

Zhang et al. (2016) discovered that by suppressing the expression of rspo2, an upstream activator of the Wnt/β-catenin signaling pathway, the AhR signaling pathway triggered by PM2.5 can mediate aberrant expression of early developmental genes in zebrafish. Moreover, the AhR/ARNT complex has the ability to function as an E3 ubiquitin ligase and directly suppress β-catenin activity, which stops it from entering the nucleus and controls the transcription of genes important for development. This regulation is definitely not one-way, since it has also been shown that β-catenin inhibits the AhR signaling pathway by increasing the transcriptional levels of genes that encode genes related to the aryl-hydrocarbon receptor repressor (AhRR).

As a promiscuous receptor, the AhR has hundreds of potential activators and antagonists. A number of environmental pollutants, including mepanipyrim, trichloroethylene, bisphenol A, S, and F, have been found to be AhR agonists and to mediate the receptor's multiple negative effects through this pathway showed in a toxicological investigation that dibutyl phthalate, a common PAE, causes necrosis in human granulosa cells by activating the AhR signaling pathway through gene knockout and chromatin immunoprecipitation methods. It is also unknown whether DEHP, a significant member of the PAEs family, has AhR agonistic activity and uses this pathway to mediate developmental toxicity.

Conclusion

To sum up, this research validates that early cardiac developmental and functional defects in zebrafish are mediated by DEHP. Among these, DEHP's activation of AhR is partially responsible for the cardiac oxidative stress it causes. Furthermore, one of the primary ways that DEHP causes cardiac developmental abnormalities appears to be the interaction between the AhR and Wnt/β-catenin signaling pathway. Notably, AhR appears to be exclusively implicated in cardiac developmental defects mediated by DEHP.

References

1. Shahri E, Velayatzadeh M, Sayadi MH (2019) Evaluation of particulate matter PM2.5 and PM10 (Case study: Khash cement company, Sistan and Baluchestan). JH&P 4: 221-226.
2. Velayatzadeh M (2020) Introducing the causes, origins and effects of dust in Iran. JH&P 5: 63-70.
3. Velayatzadeh M (2020) Air pollution sources in Ahvaz city from Iran. JH&P 5: 147-152.
4. Stinson JM, Mattsson JL (1970) Tolerance of rhesus monkeys to graded increase in environmental CO2- Serial changes in heart rate and cardia rhythm. Aerosp Med 42: 78-80.
5. Schaefer KE, Hastings BJ, Carey CR, Nichols G (1963) Respiratory acclimatization to carbon dioxide. J Appl Physiol 18: 1071-1078.
6. Neil B, Hampson MD (2011) Residential carbon monoxide poisoning from motor vehicles. Am J Emerg Med 29: 75-77.
7. Borojerdnia A, Rozbahani MM, Nazarpour A, Ghanavati N, Payandeh K (2020) Application of exploratory and Spatial Data Analysis (SDA), singularity matrix analysis, and fractal models to delineate background of potentially toxic elements: A case study of Ahvaz, SW Iran. Sci Total Environ 740: 140103.
8. Karimian B, Landi A, Hojati S, Ahadian J, et al. (2016) Physicochemical and mineralogical characteristics of dust particles deposited in Ahvaz city. Iranian J Soil Water Res 47: 159-173.
9. Goudarzi G, Shirmardi M, Khodarahmi F, Hashemi-Shahraki A, Alavi N, et al. (2014) Particulate matter and bacteria characteristics of the Middle East Dust (MED) storms over Ahvaz, Iran. Aerobiologia 30: 345-356.
10. Omri A (2013) CO_2 emissions, energy consumption and economic growth nexus in MENA countries: Evidence from simultaneous equations models. Energy Economics 40: 657-664.