Research Paper

PCB A1254 Exposure Induces Inflammation, Metabolic Dysregulation and HIF-1α Activation in Experimental Rats

G.V. Venkatakarthikeswari[1], J. Selvaraj[2]

[1]Undergraduate, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, Tamil Nadu, India

Email: VenkataKarthikeswarigv@gmail.com

[2]Assistant Professor, Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, Tamil Nadu, India

ABSTRACT

Objective

Polychlorinated biphenyls (PCBs) are persistent environmental pollutants associated with metabolic disorders, inflammation, and renal toxicity. Hypoxia-inducible factor (HIF) signaling pathways regulate erythropoietin synthesis and cellular adaptation to hypoxia. The present study aimed to evaluate PCB-induced renal damage and its effect on erythropoietin levels through HIF signaling pathways in experimental rats.

Methods

Adult male Albino Wistar rats weighing 150–180 g were divided into control and PCB-treated groups. PCB A1254 was administered intraperitoneally at a dose of 2 mg/kg body weight for 30 days. Fasting blood glucose and serum insulin levels were estimated. Messenger RNA expression levels of HIF-1α, TNF-α, and IL-6 were analyzed using real-time polymerase chain reaction (RT-PCR). Cytokine levels were determined by enzyme-linked immunosorbent assay methods. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test.

Results

PCB-treated rats demonstrated significantly elevated fasting blood glucose and serum insulin levels compared to control rats ($p<0.05$). Expression levels of inflammatory cytokines TNF-α and IL-6 were markedly increased in PCB-exposed rats. HIF-1α expression was significantly upregulated, indicating activation of hypoxic signaling pathways. Amplification and melt curve analysis confirmed successful gene amplification up to 40 PCR cycles. PCB exposure induced inflammatory responses, metabolic dysregulation, and renal hypoxic stress.

Conclusion

PCB exposure causes significant renal injury through inflammatory and hypoxia-mediated mechanisms. Altered HIF signaling pathways may interfere with erythropoietin synthesis and contribute to renal dysfunction. Chronic PCB exposure may therefore increase the risk of metabolic and renal complications.

Keywords: Polychlorinated biphenyls; HIF signaling; Erythropoietin; Renal damage; TNF-α; IL-6.

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INTRODUCTION :

Polychlorinated biphenyls (PCBs) are synthetic chlorinated aromatic hydrocarbons that were extensively used in industrial applications due to their thermal stability and lipophilic nature. Although the production of PCBs has been banned in several countries, they continue to persist in the environment because of their resistance to degradation and bioaccumulation in biological systems.[1] Human exposure to PCBs commonly occurs through contaminated food, water, and air. Several studies have demonstrated that PCB exposure is associated with oxidative stress, endocrine disruption, inflammation, metabolic dysfunction, and organ toxicity.[2] Chronic PCB exposure may adversely affect hepatic, cardiovascular, neurological, and renal systems. Epidemiological evidence has also linked PCBs with diabetes mellitus and chronic kidney disease.[3] The kidney is highly susceptible to hypoxic injury because of its elevated metabolic demand and oxygen consumption. Hypoxia-inducible factors (HIFs) are important transcriptional regulators responsible for cellular adaptation during hypoxic conditions.[4] HIF signaling pathways regulate genes involved in angiogenesis, glucose metabolism, erythropoiesis, and cell survival. Among the HIF family, HIF-1α and HIF-2α play major roles in maintaining oxygen homeostasis.[5] Under hypoxic conditions, stabilization of HIF proteins stimulates erythropoietin synthesis in renal peritubular interstitial cells. Erythropoietin is a glycoprotein hormone primarily synthesized by the kidneys and is essential for erythropoiesis.[6]

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)

contribute significantly to renal inflammation and metabolic disturbances.[7] PCB-induced oxidative stress and inflammatory responses may interfere with HIF signaling pathways and erythropoietin regulation, resulting in renal dysfunction. HIF proteins consist of oxygen-sensitive α-subunits (HIF-1α, HIF-2α, and HIF-3α) and constitutively expressed β-subunits. HIF-1α predominantly regulates glycolytic metabolism under hypoxic conditions, whereas HIF-2α plays a major role in erythropoietin synthesis and vascular remodelling (8,9). Under hypoxic conditions, HIF stabilisation promotes EPO production in renal interstitial fibroblast-like cells, thereby stimulating erythropoiesis and improving oxygen delivery to tissues (10).Erythropoietin regulates red blood cell production in the bone marrow and maintains tissue oxygenation (11). In chronic kidney disease, impaired renal function can reduce EPO synthesis, resulting in anaemia. Previous studies have suggested that PCB exposure induces oxidative stress, inflammation, apoptosis, and cellular toxicity in renal tissues, potentially interfering with HIF signalling and erythropoietin production (12,13).

PCB exposure has also been implicated in metabolic dysregulation and the development of type 2 diabetes mellitus. Elevated inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) contribute to insulin resistance and renal injury (14,15). Therefore, understanding the relationship between PCB exposure, HIF signalling, inflammation, and erythropoietin regulation is important for elucidating the mechanisms underlying PCB-induced renal damage. Therefore, the present study aimed to investigate the impact of PCB exposure on fasting blood glucose, serum insulin, inflammatory cytokines, and HIF signaling pathways in experimental rats.

MATERIALS AND METHODS

Chemicals

All chemicals and reagents used in the present study were purchased from Sigma Chemical Company (St. Louis, MO, USA), Invitrogen (USA), Eurofins Genomics India Pvt. Ltd. (Bangalore, India), New England Biolabs (USA), and Promega (USA).

Experimental animals

Adult male Albino Wistar rats weighing 150–180 g were obtained from the Biomedical Research Unit and Laboratory Animal Centre (BRULAC), Saveetha Dental College and Hospitals, Chennai, Tamil Nadu, India. Animals were maintained under controlled laboratory conditions at 21±2°C with a 12 h light/dark cycle and were provided standard pellet diet and water ad libitum.

Ethical approval

The study protocol was approved by the Institutional Animal Ethical Committee (IAEC), Saveetha Dental College and Hospitals, SIMATS, Chennai.

Approval number: BRULAC/SDCH/SIMATS/IAEC/8-2021/086.

Experimental design

Animals were randomly divided into two groups:

Group I:

Control rats receiving normal saline.

Group II:

PCB-treated rats receiving PCB A1254 (2 mg/kg body weight) intraperitoneally for 30 days.

At the end of the experimental period, rats were sacrificed and blood samples were collected for biochemical analysis. Renal tissues were isolated for molecular studies.

Estimation of fasting blood glucose and serum insulin

Fasting blood glucose levels were estimated using a glucometer after overnight fasting. Serum insulin levels were determined using commercially available ELISA kits according to the manufacturer's instructions.

RNA isolation and RT-PCR analysis

Total RNA was isolated from renal tissues using TRIzol reagent according to the manufacturer's protocol. Complementary DNA synthesis was performed using reverse transcriptase enzymes. Quantitative real-time polymerase chain reaction was carried out for HIF-1α, TNF-α, and IL-6 genes using specific primers. Relative gene expression was calculated using the comparative Ct method.

The outcome of amplification and melt curve analysis reached up to 40 PCR cycles, and the obtained data were plotted graphically by the PCR system. The amplification curve was utilized to determine relative quantification of gene expression levels.

List of primers used in the present study:

HIF-1

FW: 5'-AAG TCT AGG GAT GCA GCAC-3''

RW: 5'-CAA GAT CAC CAG CAT CTAG-3'

TNF-α

FW: 5'-GTC GTA GCA AAC CAC CAA GC-3'

RW: 5'-TGT GGG TGA GGA GCA CAT AG-3'

IL-6

FW: 5'-GTG AGA AGT ATG AGA AGT GTG A-3'

RW: 5'-GCA GGA TGA GAA TGA TCT TTG-3'

β- actin

FW: 5'-GAG ACC TCC AAC ACC CCA GCC-3'

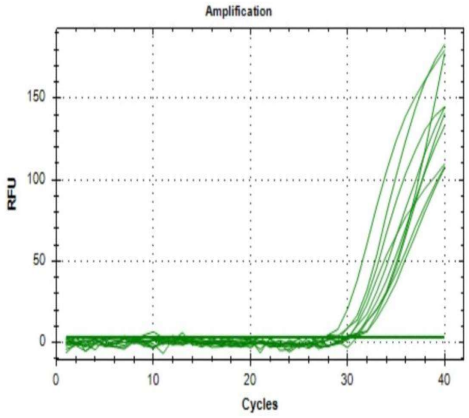
RW: 5'-GGC CAT CTC TTG CTC GAA GTC-3'

Statistical analysis

Data are presented as mean±SEM. Statistical analysis was performed using GraphPad Prism software (GraphPad, San Diego, CA, USA). One-way ANOVA followed by Tukey's multiple comparison test was used for intergroup comparison. A value of $p<0.05$ was considered statistically significant.

RESULT

The amplification and melt curve analyses were successfully completed up to 40 PCR cycles, and the obtained data were plotted graphically by the PCR machine for relative quantification analysis. PCB-treated rats showed significantly elevated fasting blood glucose levels compared with the control group (Chart 1). Similarly, serum insulin levels were significantly increased in PCB-exposed rats when compared with control rats (Chart 2). The mRNA expression levels of TNF-α were markedly higher in PCB-treated rats than in the control group (Chart 3). Likewise, IL-6 mRNA expression levels were significantly elevated in the treated rats compared with the control rats (Chart 4). In addition, HIF-1α mRNA expression levels were noticeably increased in PCB-treated rats when compared with the control group (Chart 5). These findings indicate that PCB exposure induces metabolic disturbances, inflammatory responses, and activation of HIF signalling pathways.



GRAPH : Melt and Amplification curves analysis.

The melt and amplification curve analysis confirmed successful amplification of the target genes after 40 PCR cycles. The amplification plots showed increased fluorescence intensity with increasing cycle numbers, indicating successful gene expression analysis. Relative quantification of gene expression was calculated from the amplification and melt curve data.

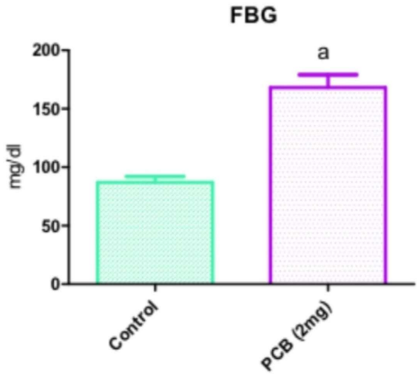


Chart 1: Fasting blood glucose (FBG)

The PCB-treated rats showed a significant increase in fasting blood glucose levels when compared with the control group. This finding suggests that PCB exposure may impair glucose metabolism and contribute to hyperglycaemic or diabetic-like alterations in the experimental animals.

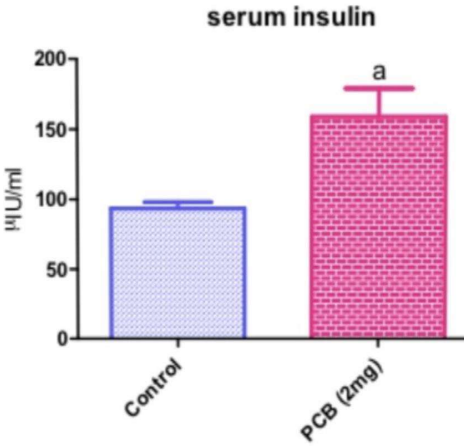


CHART 2: Serum insulin

Serum insulin levels were significantly elevated in PCB-exposed rats compared with control rats. The increase in insulin levels indicates the possible development of insulin resistance following PCB exposure.

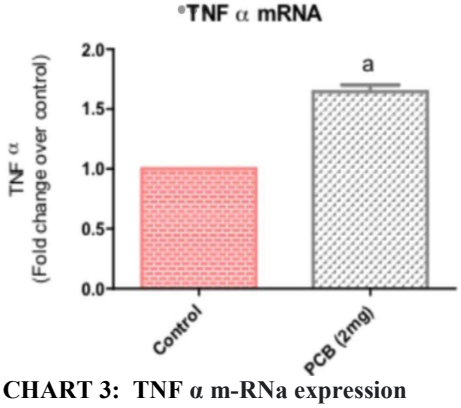


CHART 3: TNF α m-RNa expression

The mRNA expression levels of TNF-α were significantly increased in PCB-treated rats compared with the control group. This result indicates that PCB exposure induces inflammatory responses and promotes the expression of pro-inflammatory cytokines.

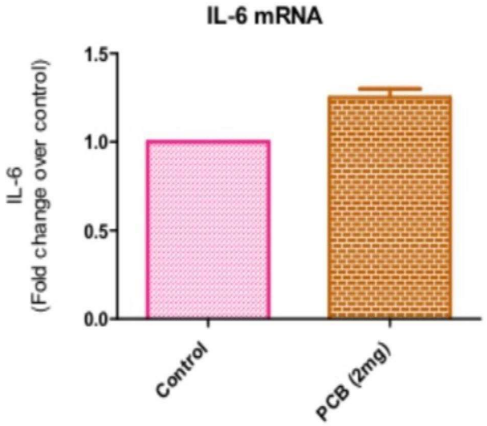


CHART 4: IL-6 m-Rna expression

The mRNA expression levels of IL-6 were markedly elevated in PCB-treated rats when compared with control rats. Increased IL-6 expression suggests enhanced inflammatory activity associated with PCB-induced renal and metabolic stress.

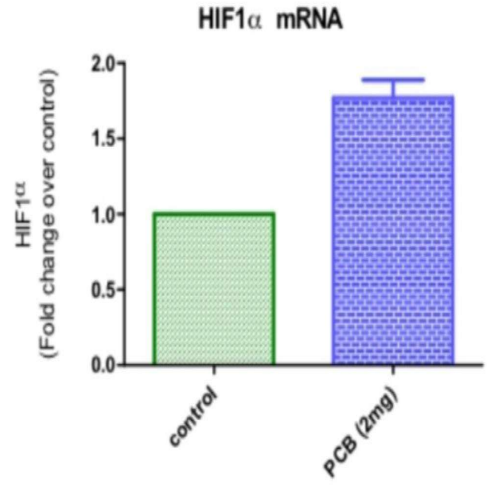


CHART 5: HIF1α m-Rna expression

HIF-1α mRNA expression levels were significantly higher in PCB-treated rats compared with the control group. This result indicates activation of hypoxia-related signalling pathways following PCB exposure, suggesting the presence of cellular stress and possible hypoxic injury in renal tissues.

DISCUSSION

PCBs are persistent environmental pollutants capable of inducing oxidative stress, inflammation, and metabolic abnormalities.[8] In the present study, PCB-treated rats demonstrated significantly elevated fasting blood glucose and serum insulin levels, suggesting impaired glucose metabolism and insulin resistance. Previous studies have reported that persistent organic pollutants contribute to the development of diabetes mellitus through inflammatory and oxidative mechanisms.[9] PCB exposure may impair insulin signaling pathways and increase inflammatory cytokine production, thereby contributing to metabolic dysfunction. Previous studies have reported that PCB congeners such as PCB-153 and PCB-77 induce oxidative stress, apoptosis, and reduced cell viability in hepatic and renal cell lines (12,16,17). Kidney cells appear to be particularly susceptible to PCB toxicity due to their high metabolic activity and increased sensitivity to oxidative injury. The present findings support earlier evidence indicating that PCB exposure contributes to renal inflammation and cellular stress (18).

The increased expression of TNF-α and IL-6 observed in this study further confirms the pro-inflammatory effects of PCBs. These cytokines are known to play important roles in the pathogenesis of renal injury, insulin resistance, and chronic inflammatory diseases (14,15). Persistent inflammatory activation may contribute to progressive renal dysfunction and altered cellular oxygen homeostasis. Hypoxia-inducible factors are critical regulators of the cellular response to hypoxia. In the present study, HIF-1α expression was significantly elevated in PCB-treated rats, indicating activation of hypoxia-responsive pathways. Increased HIF signalling may represent a compensatory response to renal hypoxia and oxidative stress induced by PCB toxicity (19,20).

Erythropoietin synthesis is tightly regulated by HIF signalling, particularly HIF-2α, which plays a major role in renal erythropoietin production. Impairment of renal function due to PCB exposure may disrupt normal erythropoietin synthesis, thereby contributing to anaemia associated with chronic kidney disease (21). Previous studies have demonstrated that inhibition of HIF-mediated erythropoietin regulation adversely affects erythropoiesis and oxygen transport (22). In addition to renal injury, PCB exposure has also been associated with metabolic disorders such as diabetes mellitus. Chronic inflammation, oxidative stress, and altered insulin signalling pathways may collectively contribute to PCB-induced metabolic dysfunction (15). The present findings support the hypothesis that PCB-mediated inflammatory and hypoxic responses

are closely linked to renal and metabolic abnormalities.

Although the present study primarily evaluated HIF-1α expression, future investigations should focus on HIF-2α and direct erythropoietin quantification to better understand the mechanistic relationship between PCB exposure and renal anaemia. Further molecular studies are necessary to identify the precise signalling pathways involved in PCB-induced renal toxicity.

CONCLUSION

The present study demonstrated that PCB exposure induces significant metabolic and renal alterations through inflammatory and hypoxia-mediated mechanisms. Elevated expression of TNF-α, IL-6, and HIF-1α indicates activation of inflammatory and hypoxic signaling pathways in renal tissues. PCB-induced renal injury may interfere with erythropoietin synthesis and contribute to renal dysfunction. Further experimental and clinical studies are required to investigate the direct relationship between PCB exposure, HIF signalling, and erythropoietin synthesis, which may provide novel therapeutic insights into PCB-associated renal diseases.

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AUTHORS' CONTRIBUTIONS

G.V. Venkatakarthikeswari contributed to study design, data collection, analysis, and manuscript preparation. J. Selvaraj supervised the study, critically reviewed the manuscript and contributed to methodology and molecular analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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