ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of the Effects of Formaldehyde Exposure on BDNF and FGF23 Levels in Kidney Tissues of Rats

Formaldehit Maruziyetinin Sıçanların Böbrek Dokularında BDNF ve FGF23 Düzeyleri Üzerine Etkilerinin Araştırılması

Feyza Aksu, Ramazan Fazıl Akkoç, Ahmet Kavaklı

Department of Anatomy, Faculty of Medicine, Fırat University, Elazıg, Türkiye

ABSTRACT

Aim: *Formaldehyde (FA) is a highly toxic chemical agent that can easily turn into gas at room temperature. It has a wide range of uses. Anatomists, pathologists, and histologists are frequently exposed to FA due to their areas of practice. Brain-derived neurotrophic factor is a protein secreted from the central nervous system and peripheral tissues that support the differentiation and growth of newly formed nerve cells and synapses. It is proven to be expressed in renal glomeruli. FGF23 is a bone-derived hormone that regulates phosphate and calcium homeostasis. It is a critical component of the abnormal mineral metabolism that complicates chronic kidney disease. This study investigates the effect of FA exposure on 3BDNF and FGF23 levels in rat kidney tissue.*

Material and Methods: *The study included 14 male Spraque-Dawley rats (7 animals in each group) aged between 8 and 10 weeks. During the experiment, the rats in the control group were exposed to natural atmospheric air in a glass bell jar. The rats in the FA group inhaled 10 ppm 8 h/day FA in a glass bell jar 5 days a week (excluding Saturdays and Sundays) for 4 weeks. At the end of the experiment, the rats were decapitated, and their kidneys were removed. Kidney tissues were homogenized and tested using the ELISA method.*

Results: *It was observed that BDNF levels significantly decreased and FGF23 levels significantly increased in the kidney tissues of FA-exposed rats compared to the control group.*

Conclusions: *This study first demonstrated the effect of exposure to FA on FGF23 and BDNF levels in rat kidney tissue. This study will contribute to future research on oxidants that increase FGF23 and BDNF expression or antioxidants that target their reduction. Accordingly, we consider it will also contribute to public health.*

Key words: *formaldehyde exposure; FGF23; BDNF; kidney; rat*

ÖZET

Amaç: *Formaldehid (FA) oda sıcaklığında gaz haline rahatlıkla geçebilen, geniş kullanım alanı olan, oldukça zehirli kimyasal bir ajandır. Anatomist, patolog ve histologlar işi gereği FA'ya devamlı maruz kalmaktadır. BDNF, hem merkezi sinir sistemi hem de periferik dokulardan salgılanan, yeni oluşan sinir hücresi ve sinapsların farklılaşmasını, büyümesini destekleyen; böbrek glomerüllerinde eksprese edildiği gösterilmiş bir proteindir. FGF23, fosfat ve kalsiyum homeostazisini düzenleyen kemik kaynaklı bir hormondur. Kronik böbrek hastalığını karmaşık hale getiren anormal mineral metabolizmasının kritik bir bileşeni olarak ortaya çıkmıştır. Bu çalışmanın amacı FA maruziyetinin sıçan böbrek dokusunda BDNF ve FGF23 düzeylerini nasıl etkilendiğini araştırılmasıdır.*

Gereç ve Yöntem: *Çalışmada Spraque-Dawley cinsi 8–10 haftalık 14 adet (her grupta yedi hayvan) erkek sıçan kullanıldı. Kontrol grubundaki sıçanlar deney süresince cam fanus içerisinde normal atmosfer havasına maruz bırakıldı. Formaldehid grubundaki sıçanlar deney süresince cam fanus içerisinde solunum yolu ile haftada beş gün (cumartesi, pazar hariç) dört hafta 10 ppm sekiz saat/gün FA'ya maruz bırakıldı. Deney sonunda hayvanlar dekapite edilip böbrekleri alındı. Böbrek dokuları homojenize edilip elisa yöntemi ile çalışıldı.*

Bulgular: *FA'ya maruz kalan sıçanların böbrek dokularında BDNF düzeylerinin kontrol grubuna kıyasla önemli ölçüde düştüğü bulunurken, FGF23 düzeylerinin ise kontrol grubuna göre istatistiksel olarak anlamlı arttığı tespit edildi.*

Sonuç: *Bu çalışmada FA maruziyetinin sıçan böbrek dokusunda FGF23 ve BDNF düzeylerine etkisi ilk kez gösterilmiştir. Bu çalışmanın, ileride yapılacak FGF23 ve BDNF ekspresyonunu artıran oksidan veya azaltılmasını hedef alan antioksidanların araştırılmasına fayda sağlayacağı kanaatindeyiz. Böylelikle halk sağlığına katkıda bulunacağı kanaatindeyiz.*

Anahtar kelimeler: *formaldehid maruziyeti; FGF23; BDNF; böbrek; rat*

İletişim/Contact: *Feyza Aksu, Department of Anatomy, Faculty of Medicine, Fırat University, Elazıg, Türkiye* • ***Tel:*** *0536 720 55 02* • ***E-mail:*** *feyza-aksu@hotmail.com* • ***Geliş/Received:*** *18.03.2024* • ***Kabul/Accepted:*** *08.07.2024*

ORCID: *Feyza Aksu: 0000-0001-8595-0010* • *Ramazan Fazıl Akkoç: 0000-0002-0559-8932* • *Ahmet Kavaklı: 0000-0003-0754-8901*

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Introduction

Formaldehyde (FA), a common metabolite found in all mammals, is a colorless gas highly soluble in water, which has a pungent odor and is an irritant in pure form. FA is an essential chemical with broad commercial use. It has acute and chronic effects on humans. FA is used as a tissue protector and bactericide in medicine. Occupational exposure applies to individuals and users at manufacturers of products containing FA[1,2]. FA is known to have adverse effects on the skin, eyes, liver, kidneys, and the nervous, reproductive, digestive, and respiratory systems[3,4].

The brain-derived neurotrophic factor (BDNF) is a protein secreted by the central nervous system and peripheral tissues and belongs to the neurotrophin family. It supports the differentiation and growth of newly formed nerve cells and synapses while maintaining the viability of existing neurons. It was first isolated from pig brain tissue in 1982 and detected in human blood in 1995. Brain-derived neurotrophic factor protein is reported in the brain areas where learning, memory, and high-level thinking functions are performed, namely the hippocampus, cortex, and prefrontal cortex[5]. Brain-derived neurotrophic factor is also peripherally synthesized by vascular endothelial cells, platelets, leukocytes, monocytes, and T and B lymphocytes. In addition, BDNF mRNA expression has been reported in the kidney, heart, lung, bladder, large vessels, spleen, visceral epithelial cells, and smooth muscle cells[6]. By immunofluorescent staining, BDNF is found to be expressed in glomeruli of normal human kidney sections, especially in podocytes and parietal epithelial cells, to a lesser extent. Brain-derived neurotrophic factor is suggested to serve as a new potential biomarker for glomerular kidney injury[7]. Studies have also revealed that BDNF has an anti-apoptotic effect in the kidney[8,9].

The fibroblast growth factor 23 (FGF23) gene encodes a 32 kDa glycoprotein of 251 amino acids secreted by osteocytes and bone marrow stromal cells. Unlike other autocrine FGFs, it circulates freely as an endocrine hormone due to the absence of heparin-binding motifs[10]. The FGF23 signaling in target organs is mediated by binding to FGF receptors (FGFRs), prominently expressed in the kidney, parathyroid gland, bones, and other tissues[11]. FGF23 is a bone-derived endocrine hormone that regulates phosphate and calcium homeostasis. FGF23 is a central regulator of normal mineral metabolism, is resistant to vitamin D, and causes hypophosphatemic rickets syndromes. It is also a critical component of the abnormal mineral metabolism that complicates chronic kidney disease[12,13]. Studies have reported a gradual increase in FGF23 levels in chronic kidney disease[14,15].

No study was found in the recent literature review to investigate the effects of FA exposure on BDNF and FGF23 levels in kidney tissue. This study aimed to investigate these effects in rat kidney tissue.

Material and Method

This study was initiated after obtaining approval from the Firat University Local Ethics Committee for Animal Experiments (2024/01–04). The study included 14 male Spraque-Dawley rats (7 in the control group and 7 in the FA-treated group) aged between 8 and 10 weeks. The rats were housed in a 100×50×20 cm glass bell jar during the 4-week experiment. Control group: The rats in this group were exposed to natural atmospheric air in a glass bell jar during the experiment. Formaldehid group: The rats in this group inhaled 10 ppm 8 h/day FA in a glass bell jar 5 days a week (excluding Saturdays and Sundays) for 4 weeks during the experiment[16]. At the end of the experiment, the rats were decapitated, and their kidneys were removed. Renal tissue supernatants were prepared by harvesting 100 mg of fresh kidney tissue from each tissue and homogenized in phosphate buffer[17]. Homogenates were centrifuged at 4°C for 5 minutes, and the supernatants were transferred to Eppendorf tubes. In the renal tissue supernatants, the BDNF and FGF23 levels were determined by the ELISA method using rat BDNF and FGF23 ELISA kits supplied by Sunred Biological Technology Co. Ltd. (Shanghai, CHINA) as specified in the manufacturer's catalog (catalog no; BDNF: 201–11–0477, FGF23:201–11–0171) and per the study procedures.

Statistical Analysis

All values were expressed as mean ± standard error. The conformity with the normal distribution was examined through Shapiro Wilk test. Statistical evaluation was performed using the independent sample t-test. For all analyses, $P < 0.05$ was considered to be statistically significant. The IBM Statistical Package for Social Sciences (SPSS) program version 22.0 for Windows (licensed by Firat University, Elazig, Türkiye), was used for data analysis.

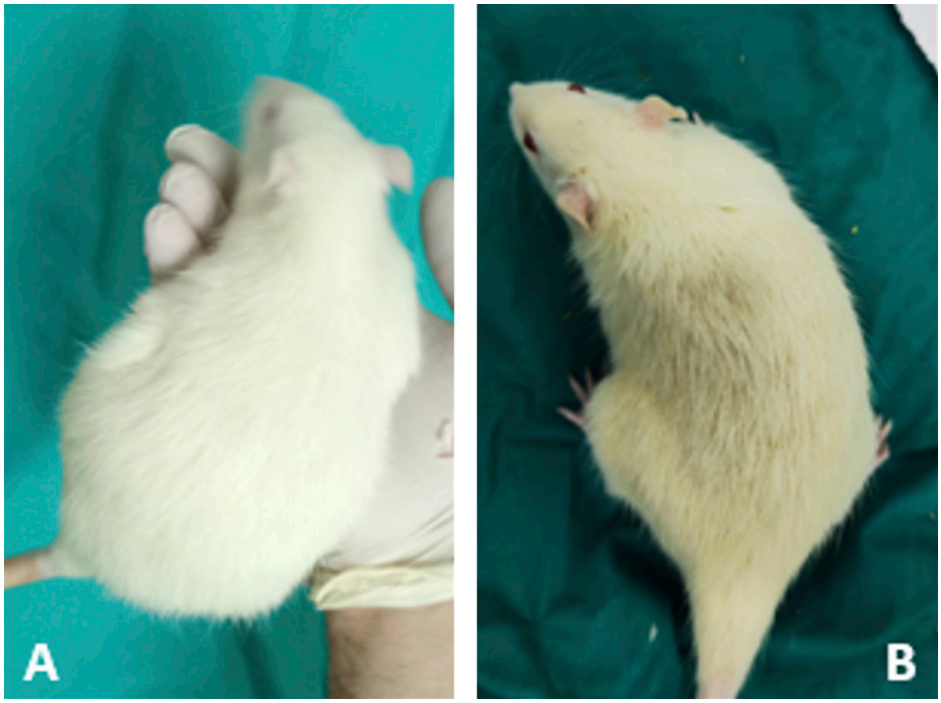

Figure 1. *(A) Control group rat with white fur. (B) FA group rat with yellow fur.*

Results

The FA exposure value measured at different hours during the study period was 10.20±0.22 ppm. During the four-week study, the hairs of the rats in the control group remained white, while yellowing was observed in the hairs of the rats in the FA group (Figure 1). In addition, the rats in the FA group exhibited slower movements and more frequent nose cleaning, blinking, and licking.

The BDNF levels were significantly decreased, while FGF23 levels were significantly increased in the kidney tissues of the rats exposed to FA compared to the control group ($p<0.05$) (Table 1).

Table 1. *Kidney tissue FGF23 and BDNF levels*

	FGF23 (pg/ml) median ± standard error	BDNF (ng/ml) median ± standard error
FA group	209.3± 63.57*	1.07± 0.08**
Control group	123.1± 33.83	1.45± 0.12

* When compared with the control group p=0.003
** When compared with the control group p=0.032

Discussion

In the body, most of the BDNF production occurs in the nervous system. Brain-derived neurotrophic factor is also secreted from the kidneys. Studies have provided evidence that BDNF may be a potential marker in patients with chronic kidney disease. In patients with chronic kidney disease, BDNF may be another marker associated with insulin resistance, sarcopenia, depression, oxidative stress, and inflammation[18]. A previous study reported that BDNF expression was suppressed by cisplatin in normal rat kidneys[13]. Ge et al.[19] investigated the effect of FA toxicity on brain BDNF levels and reported that exposure to FA caused a statistically significant decrease in brain BDNF levels. Similar to the study conducted by Ge et al., exposure to FA significantly decreased BDNF levels in kidney tissue in the present study. The literature review revealed no other study investigating the effect of exposure to FA on BDNF levels in kidney tissue.

FGF23, first discovered in the mouse brain, is an endocrine hormone secreted by bone and stimulates phosphate excretion in the kidneys. In the literature, increased levels of FGF23 were reported in chronic kidney disease, leading to left ventricular hypertrophy and autosomal dominant hypophosphatemic rickets[20,21]. Previous studies reported that FGF23 levels increased as the glomerular filtration rate decreased in children and adults with chronic kidney disease[14,22]. In the present study, exposure to FA led to a statistically

significant increase in FGF23 levels in kidney tissue. No other study was found in the literature on the effect of exposure to FA on FGF23 levels in kidney tissue.

Conclusion

The literature review revealed no study investigating the effect of exposure to FA on FGF23 and BDNF levels in kidney tissue. This study's data showed that exposure to FA decreased BDNF levels and increased FGF23 expression in kidney tissue. This study will contribute to future research on oxidants that increase FGF23 and BDNF expression or antioxidants that target their reduction.

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Conflicts of Interests

The authors report no conflicts of interest.

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