Effects of Exposure to Phthalate Plasticizers in Food on Obesity

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Abstract. Phthalate (PAEs) is an environmental pollutant and can enter the human body through respiratory tract inhalation, skin contact, and food intake. As one of the food plasticizers, PAEs are seriously harming human health. They migrate into the food and enter the human body through the food packaging materials to affect the normal physiological metabolism of the human body. In this paper, we mainly describe how PAEs can induce obesity by interacting with nuclear receptors, inhibiting the expression of genetic epigenetic factor sirtuin, increasing the content of *Bifidobacteria* in the intestinal tract, and reducing the secretion of thyroid hormones (TH).Then, two feasible solutions were introduced. One was to control obesity by inhibiting peroxisome proliferator-activated receptor gamma (PPARγ) through celery oil seeds, and the other was to control obesity by supplementing *Bifidobacterium longum* APC1472 to improve intestinal microorganism. In conclusion, this article summarizes the latest progress in the mechanism of PAEs exposure to obesity.

Keywords: Phthalates · obesity · PPARγ · sirtuin

1 Introduction

As a metabolic disease, the prevalence of obesity has been rising in recent decades and has the potential to become a global epidemic [1, 2]. Today, more than 39% of adults are overweight and 13% are classified as obese, this figure will continue to rise in developing countries in the future. High BMI will lead to non-communicable chronic diseases such as atherosclerosis, osteoarthritis, cancer, and type II diabetes [1, 3]. Excessive calorie intake, psychotropic drugs, short sleep time, and endocrine-disrupting chemicals (EDCs) are important factors in inducing obesity [3]. PAEs is one of EDCs. PAEs are phthalates that enhance the flexibility of polymer materials (including di (2-ethylhexyl) phthalate (DEHP), diisobutyl phthalate (DiBP), butyl benzyl phthalate (BBP), etc.) [2, 4] often exist in cosmetics or perfume and enter the human body through skin contact, respiratory inhalation, and food intake [1]. Therefore, people who are constantly exposed to PAEs have an increased probability of obesity. This article mainly describes the mechanisms by which PAEs lead to human obesity in a review manner.

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2 Exposure of Phthalate in Food

Food exposure is one of the main ways PAEs enter the human body [1]. DEHP, DINP, and DnOP contained in it are usually used as food packaging materials and will enter the food through migration. Edwards and others sampled and tested hamburgers, pizza, and Tex-Mex chain stores in 2017 and 2018 respectively, then analyzed the food by gas chromatography/mass spectrometry. DNBP was detected in 81% and DEHP was found in 70% of the food. They also found that high protein (meat) foods has the highest PAEs value while it is lower in cheese or pizza [4]. Similarly, in 2019, Alp purchased PP, PVC, and other packaging materials for fish from Antalya supermarket as experimental samples (containing PAEs), stored them in a 4° environment and measured them every month. Through experimental quantitative analysis of ammonium formate, methanol and other solutions and statistical analysis by software, it is concluded that the PAEs contained in PP and PVC will migrate and the migration amount will increase with the extension of contact time with packaging materials [5]. It can be seen that PAEs can be transferred from food to human body through wrapping paper to further harm human body, and the migration amount of PAEs will be affected by other factors such as food type or contact time.

3 Phthalate-induced Obesity Mechanism

3.1 *Interaction of DEHP with the Nuclear Receptor PPARγ*

Nuclear receptors (NRs) are transcription factors that are induced by ligands and widely exist in metazoans to participate in various biological processes [6]. NRs can bind to ligands and 24 NRs have established ligands. According to different ligands, common nuclear receptors are mainly divided into hormone receptors, orphan receptors and receptors involved in fatty acid and cholesterol metabolism pathways (such as progesterone X receptor (PXR), peroxisome proliferator-activated receptor (PPAR), androstane receptor (CAR), etc.) [7] PPARγ is one of the above nuclear receptors and plays an important role in transformation of preadipocytes to mature adipocytes [1]. Monoethylhexyl phthalate (MEHP), a metabolite produced by DEHP, can interact with PPARγ. Hao and other experimenters inoculated mouse 3T3-L1 cells into the culture plate in 2012. After 2 days of growth, MEHP and 10 μg/ml insulin in different concentrations were treated for 8 days in different groups while the control group was only treated with 10 μg/ml insulin for 8 days. And then, Observation of oil red O staining and glycerol-3-phosphate dehydrogenase (GPDH) activity showed that MEHP can induce the expression of PPARγ, this can promote the 3T3-L1 transfer from preadipocytes to mature adipocytes in a dose-dependent manner [8]. Thus, it is concluded that PAEs can alter individual obesity by affecting the expression of the nuclear receptor PPARγ. Similarly, Biemann summarizes the same result [1].

3.2 Inhibition of The Genetic Epigenetic Factor Sirtuin Expression By BBP

BBP is a kind of PAEs.Sirtuins is a NAD-dependent protein deacetylase and participates in various metabolic processes [2, 9]. The inhibition of sirtuin expression by BBP is

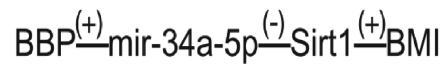

Fig. 1. BBP causes obesity mechanism

also one of the important factors causing obesity. Zhang's study showed the relationship between BBP and sirtuin protein expression for the first time. They took C3H10T1/2 cells of mice as samples. Through culture and BBP addition, they found that BBP could reduce the expression of sirtuin protein [2]. It was further observed in the experiments of Meruvu that BBP could regulate adipogenesis by affecting the expression level of mir-34a-5p. At the stage of adipogenesis, they placed mouse 3T3-L1 cells in DMSO and BBP of different concentrations. After adipocyte differentiation, they used PBS,0.02%Triton X-10, and other solutions for treatment, Finally, it was concluded that BBP exposure could increase the expression of mir-34a-5p, thereby inhibiting and damaging Sirt1 protein in mesenchymal stem cells to reduce the production of brown fat [10]. However, brown fat is inversely proportional to BMI [11] (Fig. 1). The inhibition of brown fat production can lead to the formation of obesity. Therefore, BBP can inhibit Sirt1 protein by increasing the expression of mir-34a-5p, thereby inhibiting the formation of brown fat and leading to obesity.

3.3 Changes in the Intestinal Bacteria

DEHP can affect obesity by changing the proportion of intestinal bacteria. In previous experiments, scholars divided newborns into two groups after screening. Newborns who received an intravenous infusion of DEHP were the experimental group, and those who did not receive intravenous infusion were the control group. Then, neonatal urine was collected at PND3 and blood was collected at PND8. After analysis by mathematical methods such as the Mann-Whitney U test, it was found that under the influence of intravenous injection of DEHP, the contents of *Rothia, Veillonella, Bifidobacterium, Longum,* and *Streptococcus* in the intestinal tract of newborns decreased while the *Staphylococcus* increased in comparing with the control group (Table 1) [12]. In the gut, obesity-related bacteria include *Firmicum, Bacteroides, Lactobacillus, Bifidobacterium*, etc. [13]. Among them, *Bifidobacterium* is affected by DEHP and plays an important role in intestinal obesity. It was negatively correlated with serum ghrelin. The decrease in the number of *Bifidobacteria* in obese people leads to the increase of ghrelin, which stimulates appetite and promotes the accumulation of fat, thus inducing the formation of obesity [14]. In summary, DEHP can cause obesity by reducing the amount of *Bifidobacterium* to change hormone secretion and affect metabolism.

3.4 Altered in Thyroid Hormone Secretion

Thyroid hormone (TH) is released by the thyroid gland and is involved in regulating the basic metabolism of the human body and maintaining energy balance [15, 16]. DEHP can cause obesity by disrupting TH levels. In Ye's experiment, they treated mice with corn oil and different concentrations of DEHP, and human thyroid follicular epithelial epidermal cells with NAC and different concentrations of DEHP. After detection and

Table 1. Effect of PAEs on intestinal bacteria

Bacteria type	Trend
Rothia	↓
Veillonella	↓
Bifidobacterium	↓
Longum	↓
Staphylococcus	↑
Streptococcus	↓

Fig. 2. The effect of DEHP on thyroid hormones

evaluation, it is concluded that DEHP can first produce reactive oxygen species (ROS) and induce oxidative stress. ROS is a physiological signal molecule, which will cause oxidative stress when its production and elimination are unbalanced. Oxidative stress can activate the expression of K-ras, thus activating the Akt pathway and leading to the up regulation of thyrotropin-releasing hormone receptor (TRHR), increased thyrotropin secretion (TSH) and inhibition the secretion of TH (Fig. 2) [15]. The gradual decrease of the secretion will lead to hypothyroidism, reduce metabolism and lead to obesity. In the Iossas experiment, it was found that the metabolic energy of rats with hypothyroidism decreased and the lipid increase/lipid intake ratio increased, resulting in obesity [16]. Similarly, according to the statistics of previous experiments, the weight of hypothyroid patients increased by an average of 15–30% [17]. It can be concluded that DEHP can cause human thyroid function decline and induce obesity through long-term disruption and reducing the levels of TH.

4 Solution

At present, the impact of PAEs in food on obesity. It can be treated with *Apium graveolens* oilseed extract. This is because celery oil seed extract can block the pathway of DEHP triggering obesity by inhibiting PPARγ. El-Shinnawy took adult male albino rats (weight: 110 ± 10g) as subjects and divided them into 7 groups with different additions. After low density lipoprotein (LDL) analysis, fluorescent quantitative PCR analysis, biochemical analysis and data statistics. It is found that celery seed oil can inhibit PPARγ ability to express [18]. And PPARγ can stimulate preadipocytes differentiate into mature adipocytes [1]. Therefore, celery seed oil can delay the transformation from preadipocytes to mature adipocytes by inhibiting PPARγ, and reduce the formation of mature adipocytes to block the path of PPARγ induced obesity. In addition to

obstructing PPARγ, targeted therapy for intestinal microorganisms can also be tried to directionally change the probiotic community. The number of *Bifidobacteria* in obese population will decrease, and increasing the number of *Bifidobacteria* is an effective way. Schellekens and others have tested feeding obese mice with *Bifidobacterium longum* APC1472 supplement and found that the supplement can normalize the dysregulated ghrelin and control the formation of obesity [14]. Of course, in addition to the above medical methods, the government can issue relevant measures to ensure the safety of food sources. People also need to try to reduce the frequency of taking out.

5 Conclusion

This article mainly describes the exposure of PAEs in food and the four mechanisms of inducing obesity, namely interactions of DEHP and PPAR, BBP inhibits the expression of sirtuin, changes of intestinal bacteria and changes of thyroid hormone secretion. In addition, this paper also investigated the inhibition of PPARγ by *Apium graveolens* oilseed extract to hinder the formation of adipocytes and the intake of *Bifidobacterium longum* APC1472 supplement to increase the number of *Bifidobacterium* in vivo and control the formation of obesity. Overall, the results of this study are of great significance in exploring the relationship between PAEs induced obesity and helping people to explore more solutions to control the intake of PAEs in food. However, the factors affecting obesity are complex and diverse, and other PAEs induced obesity mechanisms may be found in future studies.

References

1. Biemann, R., Blüher, M., & Isermann, B. (2021). Exposure to endocrine-disrupting compounds such as phthalates and bisphenol A is associated with an increased risk for obesity. *Best Practice & Research Clinical Endocrinology & Metabolism*, **35**(5), 101546—101546.https://doi.org/10.1016/j.beem.2021.101546
2. Zhang, J., & Choudhury, M. (2017). The plasticizer BBP selectively inhibits epigenetic regulator sirtuin during differentiation of C3H10T1/2 stem cell line. *Toxicology in Vitro*,**39**, 75–83. https://doi.org/10.1016/j.tiv.2016.11.016
3. Wright, S. M., & Aronne, L. J. (2012). Causes of obesity. *Abdominal Imaging*, **37**(5), 730–732. https://doi.org/10.1007/s00261-012-9862-x
4. Edwards, L., McCray, N. L., VanNoy, B. N., Yau, A., Geller, R. J., Adamkiewicz, G., & Zota, A. R. (2021). Phthalate and novel plasticizer concentrations in food items from U.S. fast food chains: A preliminary analysis. *Journal of Exposure Science & Environmental Epidemiology*, https://doi.org/10.1038/s41370-021-00392-8
5. Alp, A. C., & Yerlikaya, P. (2019;2020;). Phthalate ester migration into food: Effect of packaging material and time. *European Food Research & Technology*,**246**(3), 425–435. https://doi.org/10.1007/s00217-019-03412-y
6. Ishigami-Yuasa, M., & Kagechika, H. (2020). Chemical screening of nuclear receptor modulators. *International Journal of Molecular Sciences*,**21**(15), 1–19. https://doi.org/10.3390/ijms21155512
7. Toporova, L., & Balaguer, P. (2020). Nuclear receptors are the major targets of endocrine disrupting chemicals. *Molecular and Cellular Endocrinology*,**502**, 110665–110665. https://doi.org/10.1016/j.mce.2019.110665

8. Hao, C., Cheng, X., Xia, H., & Ma, X. (2012). The endocrine disruptor mono-(2-ethylhexyl) phthalate promotes adipocyte differentiation and induces obesity in mice. *Bioscience Reports*, **32**(6), 619–629. https://doi.org/10.1042/BSR20120042
9. Kong, X., Wang, R., Xue, Y., Liu, X., Zhang, H., Chen, Y., Fang, F., & Chang, Y. (2010). Sirtuin 3, a new target of PGC-1α, plays an important role in the suppression of ROS and mitochondrial biogenesis. *PloS One*, **5**(7), e11707. https://doi.org/10.1371/journal.pone.0011707
10. Meruvu, S., Zhang, J., & Choudhury, M. (2021). Butyl benzyl phthalate promotes adipogenesis in 3T3-L1 cells via the miRNA-34a-5p signaling pathway in the absence of exogenous adipogenic stimuli. *Chemical Research in Toxicology*, **34**(11), 2251–2260. https://doi.org/10.1021/acs.chemrestox.1c00115
11. Fu, T., Seok, S., Choi, S., Huang, Z., Suino-Powell, K., Eric Xu, H., Kemper, B., & Kemper, J. K. (2014). MicroRNA 34a inhibits beige and brown fat formation in obesity in part by suppressing adipocyte fibroblast growth factor 21 signaling and SIRT1 function. *Molecular and Cellular Biology*, **34**(22), 4130–4142. https://doi.org/10.1128/MCB.00596-14
12. Yang, Y., Yang, Y. S. H., Lin, I., Chen, Y., Lin, H., Wu, C., Su, Y., Yang, Y., Yang, S., & Suen, J. (2019). Phthalate exposure alters gut microbiota composition and IgM vaccine response in human newborns. *Food and Chemical Toxicology*, **132**, 110700–110700. https://doi.org/10.1016/j.fct.2019.110700
13. Million, M., Lagier, J., Yahav, D., & Paul, M. (2013). Gut bacterial microbiota and obesity. *Clinical Microbiology and Infection*, **19**(4), 305–313. https://doi.org/10.1111/1469-0691.12172
14. Schellekens, H., Torres-Fuentes, C., van de Wouw, M., Long-Smith, C. M., Mitchell, A., Strain, C., Berding, K., Bastiaanssen, T. F. S., Rea, K., Golubeva, A. V., Arboleya, S., Verpaalen, M., Pusceddu, M. M., Murphy, A., Fouhy, F., Murphy, K., Ross, P., Roy, B. L., Stanton, C., . . . Cryan, J. F. (2021; 2020;). Bifidobacterium longum counters the effects of obesity: Partial successful translation from rodent to human. Ebiomedicine, **63**, 103176–103176. https://doi.org/10.1016/j.ebiom.2020.103176
15. Ye, H., Ha, M., Yang, M., Yue, P., Xie, Z., & Liu, C. (2017). Di2-ethylhexyl phthalate disrupts thyroid hormone homeostasis through activating the Ras/Akt/TRHr pathway and inducing hepatic enzymes. *Scientific Reports*, **7**(1), 40153–40153. https://doi.org/10.1038/srep40153
16. Iossa, S., Lionetti, L., Mollica, M. P., Crescenzo, R., Barletta, A., & Liverini, G. (2001). Fat balance and serum leptin concentrations in normal, hypothyroid, and hyperthyroid rats. *International Journal of Obesity*, **25**(3), 417–425. https://doi.org/10.1038/sj.ijo.0801516
17. Krotkiewski, M. (2002). Thyroid hormones in the pathogenesis and treatment of obesity. *European Journal of Pharmacology*, **440**(2), 85–98. https://doi.org/10.1016/S0014-2999(02)01420-6
18. El-Shinnawy, N. A. (2015). The therapeutic applications of celery oil seed extract on the plasticizer di(2-ethylhexyl) phthalate toxicity. *Toxicology and Industrial Health*, **31**(4), 355–366. https://doi.org/10.1177/0748233713475515