Bisphenol A in Female Rats

Subjects: Biology

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Bisphenol A (BPA) exposure is the most prevalent in the environment. Rahman et al. (2021) summarized several confounding factors that may be directly or indirectly related to human BPA exposure and detailed the disparities between scientifically derived safe dosages of BPA and those designated as “safe” by government regulatory agencies. Exposure to BPA during early development has been associated with the prevalence of various cardiometabolic diseases including obesity, metabolic syndrome, type 2 diabetes, and cardiovascular diseases.

Keywords: resveratrol butyrate esters (RBEs) ; perinatal exposure ; obesity ; bisphenol A (BPA) ; Firmicutes/Bacteroidetes (F/B) ratio

1. Overview

Resveratrol butyrate esters (RBE) are derivatives of resveratrol (RSV) and butyric acid and exhibit biological activity similar to that of RSV but with higher bioavailability. The aim of this study was designed as an animal experiment to explore the effects of RBE on the serum biochemistry, and fat deposits in the offspring rats exposed to bisphenol A (BPA), along with the growth and decline of gut microbiota. We constructed an animal model of perinatal Bisphenol A (BPA) exposure to observe the effects of RBE supplementation on obesity, blood lipids, and intestinal microbiota in female offspring rats. Perinatal exposure to BPA led to weight gain, lipid accumulation, high levels of blood lipids, and deterioration of intestinal microbiota in female offspring rats. RBE supplementation reduced the weight gain and lipid accumulation caused by BPA, optimised the levels of blood lipids, significantly reduced the Firmicutes/Bacteroidetes (F/B) ratio, and increased and decreased the abundance of S24-7 and Lactobacillus, respectively. The analysis of faecal short-chain fatty acid (SCFA) levels revealed that BPA exposure increased the faecal concentration of acetate, which could be reduced via RBE supplementation. However, the faecal concentrations of propionate and butyrate were not only significantly lower than that of acetate, but also did not significantly change in response to BPA exposure or RBE supplementation. Hence, RBE can suppress BPA-induced obesity in female offspring rats, and it demonstrates excellent modulatory activity on intestinal microbiota, with potential applications in perinatological research.

2. Bisphenol A

Bisphenol A (BPA) exposure is the most prevalent in the environment [1]. Rahman et al. (2021) summarized several confounding factors that may be directly or indirectly related to human BPA exposure and detailed the disparities between scientifically derived safe dosages of BPA and those designated as “safe” by government regulatory agencies [2]. Exposure to BPA during early development has been associated with the prevalence of various cardiometabolic diseases [3] including obesity [4][5], metabolic syndrome [6], type 2 diabetes [5][7], and cardiovascular diseases [5][8]. The toxicokinetic studies of laboratory animals and humans after oral ingestion of BPA have similar results. BPA is rapidly absorbed from the gastrointestinal tract and undergoes first-pass conjugation to BPA-glucuronide (BPA-gluc) and BPA-sulfate (BPA-sulfate), which are biologically inactive metabolites [9][10][11][12]. The studies after oral intake of BPA or high-BPA diet in humans are consistent with animal data, confirming that the internal exposure of unbound BPA is lower after oral exposure, and BPA-gluc is the main metabolite [13][14][15][16][17][18].

Growing evidence suggests that, due to the phenolic structure of BPA, it interacts with estrogen receptors and acts as either agonist or antagonist via estrogen receptor-dependent signaling pathways [19][20][21][22]. Previous studies have demonstrated the developmental origins of the health and disease (DOHaD) hypothesis [23][24], which highlights the links between the periconceptual, foetal, and early infant phases of life and the subsequent development of adult obesity and related metabolic disorders [25][26]. The lipophilicity of BPA facilitates its entry through placental and blood–brain barriers into the foetus, where it triggers oxidative damage and nerve injury in the brain, thereby affecting brain development and causing permanent foetal brain injury [27]. In addition, previous animal studies have demonstrated that maternal and foetal exposure to BPA also damages the immune system and affects the balance of intestinal microbiota in the offspring [28][29].

There is little doubt that poor diet and lack of exercise contribute to the obesity epidemic; recent studies have identified an estrogen endocrine disrupter chemical BPA that may act as an environmental obesogen and either directly or indirectly influence fat accrual [30]. The plausible explanation may involve sex hormones, genomic and non-genomic pathway involving nuclear estrogen receptors, differing developmental pattern and/or epigenetic influence [31][32][33]. Somm et al. [34] reported that exposure to 70 μg/kg/day of BPA during pregnancy can upregulate the expression of PPARγ, C/EBPα, and LPL in abdominal adipocytes of adult female rats. In addition, body weight only increased in females, in which parametrial white adipose tissue (PWAT) weight increased about threefold. Resveratrol (RSV) can prevent BPA-induced metabolic abnormalities in offspring. Darby et al. (2019) showed that RSV can improve the placental blood flow by increasing the bioavailability of NO, can increase the activity of antioxidant enzymes in foetuses and placentas, and can reduce the rates of inflammation and cell death in placentas to ensure adequate foetal nutrition [35]. Therefore, RSV is often employed in the treatment of metabolic abnormalities and oxidative stress attributed to gestational diabetes in offspring.

The pharmacokinetic study reported by Huang et al. (2019) showed that the blood concentration of RSV peaked within 0.5 to 2 h after oral administration, followed by a rapid decline [36], indicating that RSV is unable to induce adequate pharmacological responses in pregnant women; hence, it is not an ideal clinical drug. We reported novel resveratrol butyrate esters (RBEs) and indicated the esterification of RSV with butyrate that contained RSV (~17.1%), RBE monoester (~47.1%), and RBE diester (~35.0%), which also had better hydrogen peroxide scavenging activity than RSV [37] and could effectively inhibit fatty-acid-induced lipid accumulation in HepG2 cells, with effects similar to those of RSV, but achieved at a lower dose level [38]. Butyrate, one of the short-chain fatty acids (SCFAs), can selectively promote the growth of beneficial bacteria that improve the intestinal barrier's function [39]. As RBE can be catabolised into RSV and butyrate in the body [40], we also attempted to further increase the concentration of butyrate in the intestinal tract to protect the colonic epithelial cells and nervous tissue in the brain.

Numerous studies have confirmed that intestinal microbiota and obesity are closely associated with metabolic abnormalities in hosts [41]. For example, the Firmicutes/Bacteroidetes (F/B) ratio, which is related to obesity, is lower in obese individuals than in normal individuals [42][43][44][45].

To date, there are still no obesity-related perinatological studies of RBE. Although the sex-specific effects of BPA are well documented, including the differential susceptibility of males and females to different doses of BPA [31][32][46][47][48][49], the underlying mechanism remains unclear [47]. Therefore, we performed perinatal BPA exposure studies to observe the effects of RBE supplementation on obesity-related indicators and intestinal microbiota in female rat offspring to better understand the potential applications of RBE.

3. Conclusions

Rats were exposed to BPA during the perinatal period to observe the effects of RBE supplementation on obesity-related indicators and intestinal microbiota in their female offspring to better understand the potential application of RBE. The results demonstrated that RBE supplementation can alleviate BPA-induced weight gain and body fat accumulation, optimise the concentration of blood-lipid-related markers, significantly reduce the Firmicutes/Bacteroidetes (F/B) ratio and the abundance of Lactobacillus, and increase the abundance of S24-7. In addition, RBE supplementation can also regulate the intestinal concentration of acetate in female offspring rats. In summary, RBE can suppress BPA-induced obesity in female offspring rats and exhibits excellent modulatory activity in intestinal microbiota, with potential applications in perinatological research. In the future, we will clarify the metabolism of RBE in the digestive systems of animals and its haemodynamics after absorption to further understand the potential of RBE in future applications.

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