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The effects of pre- and postnatal exposure to perfluorooctanoic acid on the expression of major reproduction-related genes in the mouse hypothalamus and gonads

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ABSTRACT

Perfluorooctanoic acid (PFOA), a ubiquitous environmental pollutant reported to be an endocrine disruptor, is used in many industrial and consumer products. Although the adverse effects of PFOA on the reproductive health of animals and humans have been widely reported, most studies have focused on assessing the anatomical features and conventional histology of adult gonads. Therefore, the molecular mechanisms activated in the hypothalamus and gonads following PFOA exposure during the pre- and postnatal periods are not clear. This study used a mouse model to evaluate the effects of PFOA exposure on the alteration of molecular mechanisms in the hypothalamus and gonads during the prenatal and postpartum periods. Changes in gene and protein expression following PFOA exposure were evaluated by quantitative polymerase chain reaction and Western blotting, respectively. Kisspeptin 1 and gonadotropin-releasing hormone expression in the hypothalamus of female and male mouse pups was significantly decreased. Additionally, Cyp17a1 expression was upregulated in male offspring testes, while Cyp17a1 and Cyp19a1 expression was downregulated in female offspring ovaries. Changes at the molecular level due to PFOA exposure in the early stages of development did not show sex-related differences in the hypothalamus; however, such differences were confirmed in the gonads. These results could be used as basic data to study the molecular mechanisms underlying the reproductive dysfunction caused by PFOA exposure in the early stages of embryonic development.

Key words: gonads; hypothalamus; perfluorooctanoic acid; postnatal; prenatal

Introduction

Several hundred metric tons of per- and polyfluoroalkyl substances have been produced and used in various ways per year for more than 70 years (LINDSTROM et al., 2011). Perfluorooctanoic acid (PFOA) is one of the most common perfluoroalkyl substances in the environment. It is an environmental pollutant that can interfere with the endocrine system (GOOSEY and HARRAD, 2011). PFOA has a perfluorinated alkyl chain of 7 carbons, making it oleophobic and hydrophobic

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and the terminal carboxylate group attached to the perfluorinated chain imparts hydrophilicity (OECD, 2006). PFOA has been widely applied as a surfactant for manufacturing water- and oil-resistant products, such as coatings for outdoor clothing, non-stick cookware, carpets, firefighting products and industrial products (BACH et al., 2016; BERGMAN et al., 2015; LINDSTROM et al., 2011). Owing to its numerous uses, PFOA is ubiquitous (BETTS, 2007). Its stable chemical structure makes it resistant to hydrolysis, photolysis, and biodegradation, allowing it to remain in the environment and animal bodies for a prolonged period (LAU et al., 2007; PREVEDOUROS et al., 2006). PFOA has been detected in human serum, cord blood, and breast milk (APELBERG et al., 2007; LLORCA et al., 2010). Its half-life in serum is 2-4 years (PREVEDOUROS et al., 2006).

PFOA is toxic to the reproductive and developmental stages of animals, causing damage to the seminiferous tubules, decreasing testosterone and progesterone levels, and increasing estradiol levels (CHAPARRO-ORTEGA et al., 2018; LAU et al., 2007; ZHANG et al., 2014). Exposure to PFOA during early development decreases sperm count and testis size, delays puberty, accelerates menopause, increases the incidence of spontaneous abortion, and causes fluctuation in testosterone, estradiol, luteinising hormone, and follicle-stimulating hormone levels (DU et al., 2019; FEI et al., 2009; KRISTENSEN et al., 2013; SONG et al., 2018; VESTED et al., 2013). Although the adverse effects of PFOA on reproduction have been reported previously, most studies have evaluated its effects on the basis of histological and anatomical features. Additionally, a limited number of studies have investigated the ability of PFOA exposure to alter molecular mechanisms in the hypothalamus and gonad regions during early-stage embryonic development, which is a critical period for endocrine system development. Therefore, in the present study, the expression of kisspeptin 1 (Kiss1) and gonadotropin-releasing hormone (GnRH) in the hypothalamus, and gonadal steroidogenic enzymes in the gonads was investigated to evaluate the effect of PFOA exposure on reproductive molecular mechanisms during the pre- and postnatal periods.

Materials and methods

Animals and PFOA treatment. Six-week-old male (n=5) and female (n=5) CrljBgi:CD-1 (ICR) mice were purchased from DBL (Eumseong, Korea). These mice were housed in polypropylene cages under a controlled temperature (20°C–25°C) and humidity (60%–70%) in a 12-h light/dark cycle. The mice were provided free access to food and water. This study was approved by the Animal Experimental Ethics Committee of Kangwon National University (KW-180705-3).

PFOA (95% purity), procured from Sigma-Aldrich (St. Louis, MO, USA), was administered orally through drinking water at a dose of approximately 1 mg kg^{-1} d^{-1}. The estimated intake was calculated on the basis of the average rate of drinking and body weight, as recorded in pilot experiments. One week after PFOA treatment, male and female mice were randomly paired to induce mating, and the mated mice (F_0) were housed individually. Drinking water laced with PFOA was provided to the mice from 1 week before pregnancy, during pregnancy, and from birth to 1 d before sacrifice. The day of birth, when the pups (F_1) were first observed, was designated postnatal day 0. The mice were sacrificed by cervical dislocation on postnatal day 49. Testis, ovary and hypothalamus tissue were collected directly from the sacrificed mice, immediately frozen in liquid nitrogen, and stored at -80 °C until analysis.

Real-time quantitative polymerase chain reaction (RT-qPCR. RNA was extracted from the testis, ovary and hypothalamus tissue using the TRIzol® RNA Isolation Reagent (Invitrogen, Carlsbad, CA, USA), according to the manufacturer›s protocol. The purity and concentration of the extracted RNA were quantified using a Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). RT-qPCR was performed with the ABI 7500 Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) using the iTaqTM Universal SYBR® Green One-Step kit (Bio-Rad, Hercules, CA, USA) with gene-specific primers (Table 1). ß-Actin was used as the control gene; relative gene expression was calculated using the $2^{-\Delta\Delta CT}$ method.

Table 1. RT-qPCR primer sequences

Gene	Primer sequences (5′→3′)	
Kiss1	Forward:	GAATGATCTCAATGGCTTCTTGG
	Reverse:	TTTCCCAGGCATTAACGAGTT
GnRH	Forward:	GGGAAAGAGAAACACTGAACAC
	Reverse:	GGACAGTACATTCGAAGTGCT
Star	Forward:	GGAACCCAAATGTCAAGGAGATCA
	Reverse:	GCACGCTCACGAAGTCTCGA
Cyp11a1	Forward:	AGCTGGGCAACATGGAGTCA
	Reverse:	CCTCTGGTAATACTGGTGATAGGC
Cyp17a1	Forward:	GATCTAAGAAGCTCAGGCA
	Reverse:	GGGCACTGCATCACGATAAA
Cyp19a1	Forward:	CTGTCGTGGACTTGGTCATG
	Reverse:	GGGGCCCAAAGCCAAATGGC
□-*Actin*	Forward:	ATGGTGGGAATGGGTCAGAAG
	Reverse:	CACGCAGCTCATTGTAGAAGG

Western blotting. Protein samples were homogenised in 10% sodium dodecyl sulphate and electrophoresed on a 10% Tris-glycine polyacrylamide gel. The separated proteins were blotted onto polyvinylidene fluoride membranes (EMD Millipore, Bedford, MA, USA). The membranes were then blocked using 5% skim milk, and incubated with primary antibodies against Kiss1 (1:500, Biorbyt, Cambridge, UK), GnRH (1:500, Biorbyt), CYP19A1 (1:300; Bioss Antibodies, Woburn, MA, USA), and CYP19A1 (1:300, Bioss Antibodies) for 2 h at room temperature. The membranes were washed in Tris-buffered saline/0.1% Tween 20 and incubated with a secondary antibody (mouse anti-rabbit IgG-horseradish peroxidase, 1:2500) for 1 h at room temperature. Specific bands were detected using the Pierce™ ECL Plus Western Blotting Substrate (Thermo Fisher Scientific), coupled with the ImageQuant LAS 500 Gel Documentation System (GE Healthcare, Little Chalfont, UK). The relative band intensity was calculated by scanning and quantifying immunoblotting data using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Statistical analyses. The results were analysed using Prism software version 7.0 (GraphPad Software, San Diego, CA, USA) and presented as means ± standard error of the mean. Statistical significance was determined using the t-test or a two-way analysis of variance, followed by the Bonferroni post-hoc test. Statistical significance was set at $P<0.05$.

Results

In this study, RT-qPCR was used to evaluate the expression of major reproduction-related genes in the testis, ovary and hypothalamus tissue after exposure to 1 mg kg^{-1} d^{-1} of PFOA during the pre- and postnatal periods. The expression of *GnRH* and *Kiss1*, which play important roles in reproductive

regulation, was decreased in both female and male hypothalami (Fig. 1A). The effects of pre- and postnatal PFOA exposure on the hypothalamus were quantified at the protein level by Western blotting. GnRH and Kiss1 expression was also decreased in both female and male mice following PFOA exposure (Fig. 1B).

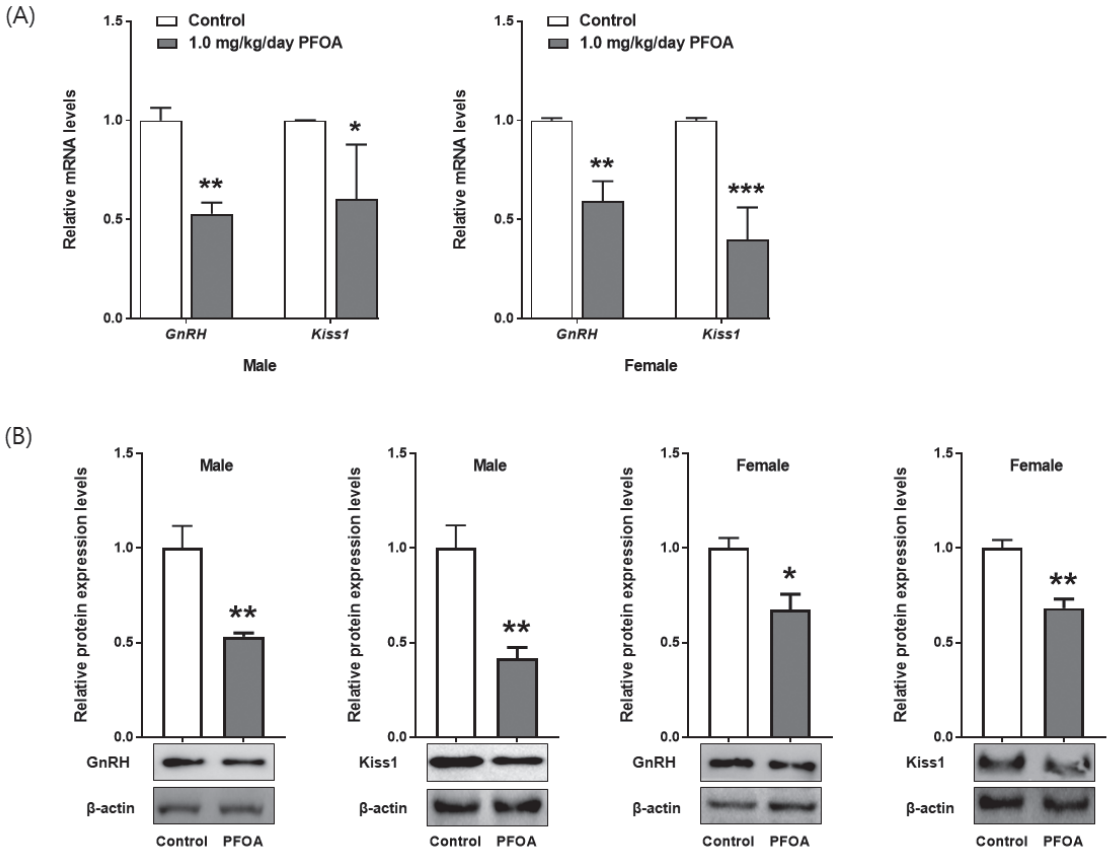

Fig. 1. The effects of perfluorooctanoic acid (PFOA) exposure on the gene and protein expression profiles of kisspeptin 1 (Kiss1) and gonadotropin-releasing hormone (GnRH) in male and female mouse pup hypothalami. (A) The effects of PFOA on gene expression. (B) The effects of PFOA on protein expression. *P<0.05, **P<0.01, and ***P<0.001.

The expression of steroid-generating enzyme-coding genes in the testes and ovaries of female and male offspring, respectively, was evaluated to determine whether PFOA exposure directly or indirectly affected the gonads at the molecular level. PFOA exposure significantly increased *Cyp17a1* expression in male mouse pups, whereas *Cyp17a1* and aromatase-coding gene (*Cyp19a1*) expression was significantly decreased in female pups (Fig. 2A). Cyp17a1 and Cyp19a1 expression in male and female mouse gonads was also evaluated. PFOA exposure significantly upregulated and downregulated Cyp17a1 and Cyp19a1 expression, respectively, in the testes of male mice (Fig. 2B). Cyp17a1 and Cyp19a1 expression was significantly decreased in the ovaries of PFOA-exposed female mice during the pre- and postnatal periods (Fig. 2B).

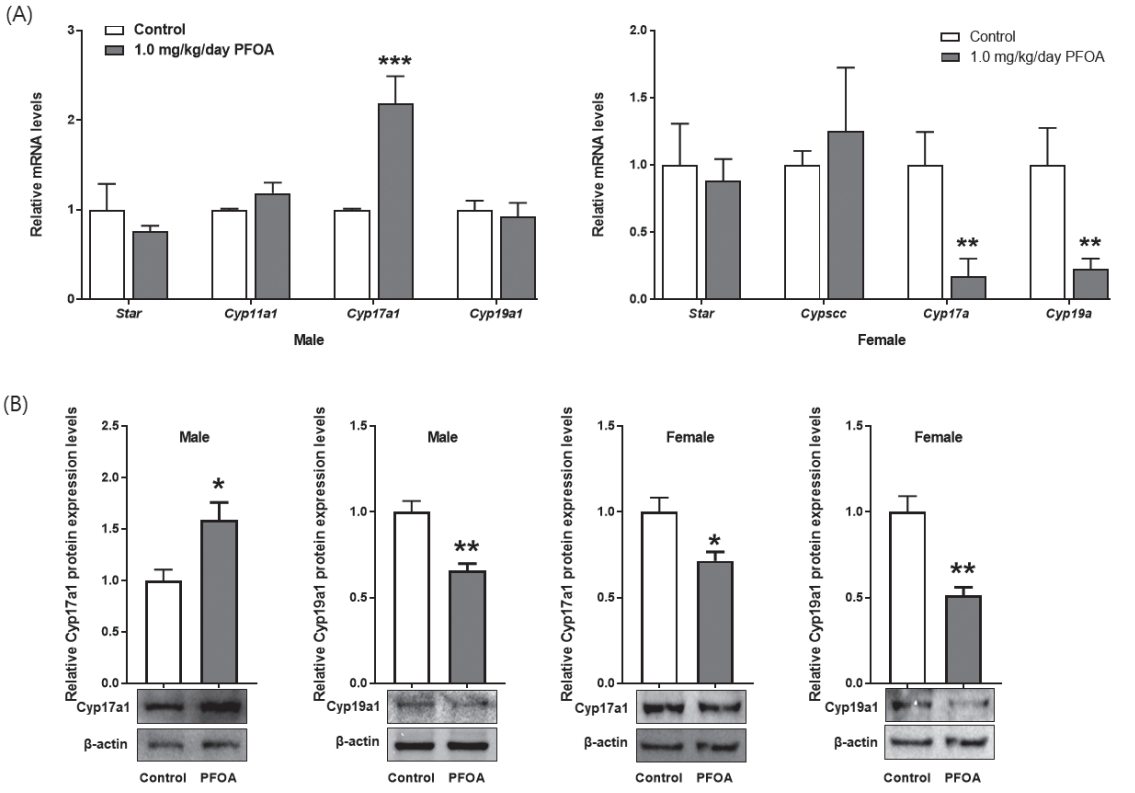

Fig. 2. The effects of perfluorooctanoic acid (PFOA) exposure on the gene and protein expression profiles of gonadal steroidogenic enzymes in the testes and ovaries of male and female mouse pups. (A) The effects of PFOA on gene expression. (B) The effects of PFOA on protein expression. *P<0.05, **P<0.01, and ***P<0.001.

Discussion

PFOA exposure during early development accelerates puberty in rodents (DU et al., 2019; LAU et al., 2006) and causes irregular oestrous cycles (DU et al., 2019). Kiss1 regulates the onset of puberty (HAMEED and DHILLO, 2010) and acts as a GnRH release regulator (NOVAIRA et al., 2012). In this study, pre- and postnatal PFOA exposure resulted in the downregulation of Kiss1 and GnRH expression in the hypothalamus of male and female mouse pups. The results confirmed a decrease in Kiss1 expression, consistent with the findings of a previous study, which reported that a decrease in *Kiss1* expression in the hypothalamus of female mice exposed to PFOA during the neonatal period promoted the onset of puberty (DU et al., 2019). Puberty acceleration due to PFOA exposure in male mouse pups during gestation may be influenced by reduced Kiss1 expression (LAU et al., 2006). GnRH is crucial for controlling puberty and the oestrous cycle (BARBIERI, 2014; PLANT, 2015). GnRH expression is also reduced following PFOA exposure, which may be the cause of the irregular oestrous cycles observed in a previous study (DU et al., 2019). Additionally, because GnRH is the central regulator of the hypothalamic–pituitary–gonadal (HPG) axis, which regulates the levels of numerous reproductive hormones, decreased GnRH expression due to PFOA exposure may contribute to various reproductive disorders.

Feedback regulatory mechanisms maintain sex hormone homeostasis along the HPG axis (MAFFUCCI and GORE, 2009; MICEVYCH et al., 2009). Changes in hormone expression in the hypothalamus can cause changes in steroid hormone production in the gonads. In the present

study, the exposure of mice to PFOA decreased GnRH expression in the hypothalamus, increased Cyp17a1 expression in the testes, and decreased Cyp19a expression in the ovaries (Fig. 2). In contrast, in a previous study, exposure to bisphenol A (BPA) increased hypothalamic *GnRH* and ovarian *Cyp19a1* expression, and decreased testicular *Cyp17a1* expression (XI et al., 2011). In the present study, the exposure of mice to PFOA, unlike BPA, decreased hypothalmic GnRH and ovarian Cyp19a1 expression, and increased testicular Cyp17a1 expression. Interestingly, both PFOA and BPA act as xenoestrogens, but the mechanisms through which they regulate GnRH expression in the hypothalamus differ. In addition, PFOA exposure affected gonad steroidogenic enzyme expression differently at mRNA and protein levels according to sex. Gender differences were also found in the tissue distribution and pharmacokinetics of PFOA, and it has been reported that these sex differences are caused by the metabolism of steroid hormones (HUNDLEY et al., 2006; KIM et al., 2016; OHMORI et al., 2003; VANDEN HEUVEL et al., 1991). Although significant effects of PFOA exposure on HPG regulatory circuits were identified in the current study, they may not necessarily be broadly reflected in humans upon PFOA exposure.

Conclusions

The results of this study suggest that pre- and postnatal PFOA exposure could interfere with Kiss1 and GnRH expression at the protein and mRNA levels in the hypothalamus, thereby affecting HPG axis homeostasis. Additionally, PFOA exposure affected gonadal steroidogenic enzyme expression at the mRNA and protein levels differently, according to gender. These results could be used as basic data to study the molecular mechanisms underlying the abnormal reproductive changes caused by pre- and postnatal PFOA exposure.

Conflict of Interest

The authors declare that there is no conflict of interest.

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SAŽETAK

Perfluorooktanska kiselina (PFOA) sveprisutna je onečišćujuća tvar za okoliš, za koju je zabilježeno da uzrokuje i endokrinopatije, a upotrebljava se u mnogim industrijskim proizvodima. Bez obzira na poznate i zabilježene nuspojave PFOA-e na reproduktivno zdravlje životinja i ljudi, većina se istraživanja usredotočuje na procjenu anatomskih histoloških značajki u spolnim žlijezdama odraslih jedinki. Molekularni mehanizmi koji se aktiviraju u hipotalamusu i spolnim žlijezdama nakon izlaganja PFOA-i stoga nisu razjašnjeni. U ovom je istraživanju upotrijebljen mišji model za procjenu učinaka izlaganja PFOA-i na promjenu molekularnih mehanizama u hipotalamusu i spolnim žlijezdama za vrijeme prijeporođajnog i poslijeporođajnog razdoblja. Promjene u ekspresiji gena i proteina nakon izloženosti PFOA-i analizirane su kvantitativnom PCR metodom i metodom Western blotting. Ekspresija kispeptina 1 i hormona koji oslobađa gonadotropin u hipotalamusu ženske i muške mladunčadi bila je znakovito smanjena. Osim toga ekpresija Cyp17a1 bila je pojačana u testisima muških potomaka, dok je ekspresija Cyp17a1 i Cyp19a1 u jajnicima ženskih potomaka bila smanjena. Kod promjena na molekularnoj razini u hipotalamusu u ranim razvojnim stadijima nije bilo razlike među spolovima, dok je kod promjena u spolnim žlijezdama povrđena razlika među spolovima. Rezultati ovog istraživanja mogli bi biti korisni kao osnovni podaci u proučavanju molekularnih mehanizama podležeće reproduktivne disfunkcije uzrokovane izloženošću PFOA-i u ranim stadijima embrionalnog razvoja.

Ključne riječi: spolne žlijezde; hipotalamus; perfluorooktanska kiselina; postnatalno i prenatalno razdoblje