Toxicology Letters 295 (2018) 1–9

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Perfluorooctane sulfonate (PFOS) can alter the hypothalamic–pituitary–adrenal (HPA) axis activity by modifying CRF1 and glucocorticoid receptors

R. Salgado-Freiría*, S. López-Doval, A. Lafuente

Laboratory of Toxicology, Sciences School, University of Vigo, Las Lagunas s/n, 32004 Ourense, Spain

ARTICLE INFO

Keywords:
Perfluorooctane sulfonate (PFOS)
Hypothalamic–pituitary–adrenal (HHA) axis
Corticotropin-releasing factor 1 receptor (CRF1r)
Glucocorticoid receptor (Gr)

ABSTRACT

Perfluorooctane sulfonate (PFOS) is an endocrine disruptor highly persistent, bioaccumulative and neurotoxic, whose presence has been detected in different compartments of the environment. The aim of this study was to investigate whether PFOS could alter the HPA axis activity by modifying the gene and protein expression of corticotropin-releasing factor 1 receptor (CRF1r) and glucocorticoid receptor (Gr). For that purpose, Sprague-Dawley adult male rats were orally treated by gavage with 0.5; 1.0; 3.0 and 6.0 mg of PFOS/kg/day for 28 consecutive days. After PFOS administration, gene and protein expression of CRF1r were analysed in the hypothalamus, hippocampus, pituitary and adrenal glands. Moreover, Gr gene and protein expression were measured in hypothalamus, pituitary gland, prefrontal cortex, amygdala and hippocampus. The reported results indicate that (1) PFOS could inhibit HPA axis activity by diminishing gene and protein expression of CRF1r in the pituitary gland; (2) PFOS inhibits Gr protein expression in both prefrontal cortex and amygdala, which could be related to the toxic effects of this contaminant in this neuroendocrine axis and finally, (3) PFOS-treated rats would try to maintain the physiological levels of corticosterone by reducing the protein expression of Gr in the pituitary gland.

1. Introduction

Perfluorooctane sulfonate (PFOS) is an anthropogenic compound with high thermal, chemical and biological stability, which makes it a perfect ingredient for many industrial applications (Kissa, 2001). Nevertheless, these characteristics also mean that PFOS is a persistent compound in the environment, not being degraded under environmental conditions (OECD, 2002). This restricted xenobiotic is currently in all environmental compartments (Liu et al., 2017). PFOS is the degradation product of more than 50 compounds (Wang et al., 2009), so it can be used as a model molecule in toxicological evaluation studies of this class of pollutants.

PFOS is accumulated in different tissues, in brain and in several endocrine glands like pituitary and adrenal glands (Austin et al., 2003). In addition, it seems to exist a relation between PFOS exposure and a number of common chronic pathologies including hypercholesterolemia (Eriksen et al., 2013; Xu et al., 2017) and thyroid disease (Chang et al., 2017; Coperchini et al., 2017), as well as an evidence of the association between PFOS and some types of cancer (Barry et al., 2013; Chang et al., 2014). In the recent literature there is also evidence that relates PFOS to other damages, such as immunotoxicity (Soloff et al., 2017), developmental effects (Wang et al., 2017), neurotoxicity (Li et al., 2017a), hepatotoxicity (Chang et al., 2017; Xu et al., 2017), and carcinogenicity (Arrieta-Cortes et al., 2017) among others.

It is well-known that PFOS exerts its toxicity at neuroendocrine level (Salgado et al., 2015, 2016), with significant toxic effects on the hypothalamic–pituitary–adrenal (HPA) axis activity (Pereiro et al., 2014) and on dopaminergic system in several limbic brain regions (Salgado et al., 2016). This neuroendocrine axis is involved in the maintenance of homeostasis (De Kloet et al., 2005), whose disruption is associated with different pathologies and altered physiological states.

The HPA axis controls its own activity through a negative feedback mechanism exercised by glucocorticoids (Keller-Wood, 2015), which limits the hypothalamic corticotropin-releasing factor (CRF) secretion and the pituitary adrenocorticotropic hormone (ACTH) release (Keller-Wood, 2015). CRF binds to its specific receptors (corticotropin-releasing factor 1 receptor or CRF1r) on pituitary gland to increase ACTH synthesis and secretion, which stimulates glucocorticoid synthesis by the adrenal gland (Fig. 1). Moreover, CRF regulates HPA axis activity through CRF1r directly in adrenal gland (Nussdorfer, 1996; Müller

* Corresponding author.
E-mail address: freiria@uvigo.es (R. Salgado-Freiría).

https://doi.org/10.1016/j.toxlet.2018.05.025
Received 19 December 2017; Received in revised form 28 March 2018; Accepted 20 May 2018
Available online 26 May 2018
0378-4274/

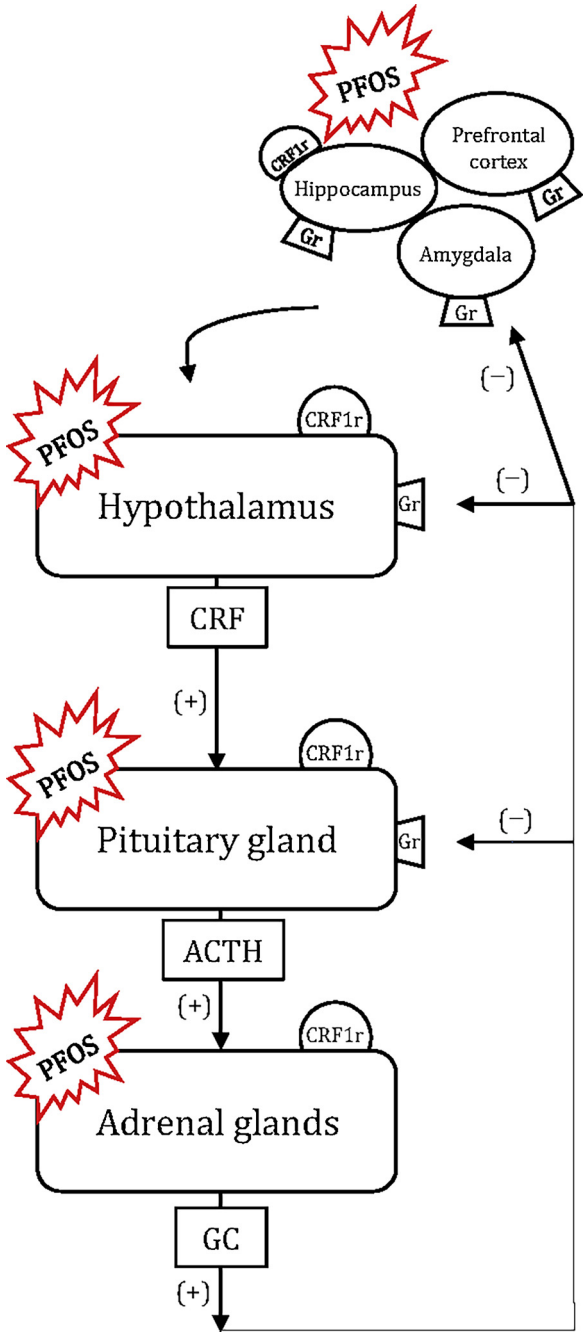

Fig. 1. Limbic-hypothalamic–pituitary–adrenal axis regulation. The hormones, neuropeptides and receptors analysed in this study are shown in this scheme. CRF: corticotropin-releasing factor; ACTH: adrenocorticotropic hormone; GC: glucocorticoids; CRF1r: CRF receptor 1; Gr: glucocorticoids receptor.

et al., 2001) and indirectly in hippocampus (Yan et al., 1998; Bagosi et al., 2015) where CRF also acts as a neurotransmitter and participates in behavioural and autonomic responses to the stress (Beery et al., 2014).

Glucocorticoids regulate their secretion by a direct action in their specific receptors (glucocorticoid receptors or Gr), thereby inhibit the synthesis and release of CRF and ACTH (Keller-Wood, 2015), and affect cerebral structures such as the limbic system (Herman et al., 2005). Feedback regulation of the HPA axis activity is dependent on the glucocorticoids action through Gr in the hypothalamic paraventricular nucleus (PVN) and in the pituitary gland, as well as in several limbic structures, mainly in the hippocampus, prefrontal cortex and amygdala (De Kloet et al., 2005). The hippocampus and the prefrontal cortex exert a negative feedback on the HPA axis through projections to the PVN, while the amygdala has a stimulatory influence on the PVN and thus the HPA axis (Ulrich-Lai and Herman, 2009).

PFOS presents toxicity on the HPA axis activity in rats (Austin et al., 2003; Zhao et al., 2011a; Pereiro et al., 2014; Li et al., 2016), mice (Zheng et al., 2009, 2011; Ribes et al., 2010), fishes (Shi et al., 2009; Mortensen et al., 2011; Du et al., 2016) and in human beings (Zhao et al., 2011a,b; Goudarzi et al., 2017). Oral PFOS exposure (at the doses of 0.5; 1.0; 3.0 and 6.0 mg PFOS/kg/day for 28 consecutive days) inhibits the overall activity of the HPA axis by decreasing the hypothalamic CRF concentration and the serum ACTH and corticosterone levels (Pereiro et al., 2014). Moreover PFOS, at these same doses, modifies CRF and adrenocorticotropic hormone receptor (ACTHr) gene expression in the hypothalamus, gene expression of proopiomelanocortin (POMC) and ACTHr in the pituitary gland and in the adrenal gland, respectively (Pereiro et al., 2014). This chemical also modifies relative weight and morphology of the adrenal gland (Pereiro et al., 2014). However, studies by other authors suggest a stimulatory effect of PFOS on the HPA axis at high doses in rodents (Austin et al., 2003; Zheng et al., 2009). Specifically, mice orally exposed to PFOS for 7 days at doses of 20 and 40 mg/kg/day show an increase in serum corticosterone concentration (Zheng et al., 2009). This same stimulation is reported in mice treated with 5 and 20 mg of PFOS/kg/day (Zheng et al., 2011). Likewise, rats treated with 10 mg PFOS/kg/day for 2 weeks exhibit an increase in serum corticosterone concentration (Austin et al., 2003). Similarly, the administration of 5 and 20 mg of PFOS/kg/day in pregnant rats results in an increase in corticosterone levels in the foetal serum (Li et al., 2016). The same effect was observed in pregnant mice with the dose of 6 mg/kg/day of PFOS (Ribes et al., 2010). On the other hand, gene expression of CRF appears to be increased in zebrafish after exposure of PFOS (200 and 400 μg/L) (Shi et al., 2009). However, the expression of this gene is not significantly altered in mice after exposure to 75 μg PFOS/kg/h for 4 h (Asakawa et al., 2007). A recent study in human beings shows that prenatal exposure to PFOS is significantly associated with glucocorticoid levels in cord blood samples (Goudarzi et al., 2017). These observed differences in the effects of PFOS on the HPA axis could be due to the wide range of doses administered of this chemical as well as to the different animal species treated.

Taking into account that: (a) PFOS inhibits CRF gene expression as well as CRF and corticosterone secretion (Pereiro et al., 2014); (b) CRF1r mediates the stimulation of the pituitary ACTH secretion by this neuropeptide (Rivier et al., 2003); (c) corticosterone regulates its own synthesis by a negative feedback in the hypothalamus and pituitary gland through its receptors (Gr) (Herman and Cullinan, 1997; Bagosi et al., 2015); as well as (d) the bidirectional relationship between the HPA axis and several limbic brain regions (hippocampus, prefrontal cortex and amygdala) (Smith and Vale, 2006), we have seen fit to evaluate the toxic effects of PFOS on the gene and protein expression of CRF1r and Gr at different levels of the HPA axis and in some limbic brain areas. More concretely after PFOS exposure, gene and protein expression of CRF1r will be determined in the hypothalamus, pituitary and adrenal glands as well as in the hippocampus. At the same time, mRNA and protein levels of Gr will be analysed in the hypothalamus, pituitary gland, prefrontal cortex, amygdala and hippocampus. The hypothalamic concentration of CRF and serum levels of ACTH and corticosterone will be also quantified.

2. Material and methods

2.1. Chemical

Perfluorooctane sulfonic acid has been used as potassium salt. It was purchased from Sigma-Aldrich (Madrid, Spain) and it was dissolved in 2.5% Tween 20, which was obtained from VWR International (Radnor,