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Inhibition effects of perfluoroalkyl acids on progesterone production in mLTC-1

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ABSTRACT

Perfluoroalkyl substances (PFASs) are a class of fluorine substituted carboxylic acid, sulfonic acid and alcohol, structurally similar to their corresponding parent compounds. Previous study demonstrated the potential endocrine disruption and reproductive toxicity of perfluorooctane sulfonic acid and perfluorooctanoic acid, two dominant PFASs in animals and humans. We explored the relationship between eleven perfluoroalkyl acids (PFAAs) with different carbon chain length and their ability to inhibit progesterone production in mouse Leydig tumor cells (mLTC-1). We found an obvious dose–response relationship between progesterone inhibition rate and PFAA exposure concentration in mLTC-1. The relative inhibition rate of progesterone by PFAAs was linearly related to the carbon chain length and molar refractivity of PFAAs. Mitochondrial membrane potential (MMP) decreased after PFAA exposure at the half-maximal inhibitory effect concentration (IC_{50}) of progesterone production in mLTC-1, while the reactive oxygen species (ROS) content increased significantly. These results imply that the inhibition effect of PFAAs on progesterone production might be due, in part, to ROS damage and the decrease in MMP in mLTC-1.

Introduction

Perfluoroalkyl substances (PFASs) are a family of man-made, highly stable and hydrophobic organic compounds, widely used in fabrics and fast-food container material sand fire-resistant foams (Frisbee et al., 2009). This organic family shares common structural and physicochemical characteristics and properties, but differs in backbone carbon chain length and functional group, the main features used to classify PFASs into perfluoroalkyl acids (PFAAs) and fluorotelomer alcohols (Buck et al., 2011). Fluorotelomer alcohols serve as precursors that can be transformed into PFAAs (Dinglasan et al., 2004). Perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs) are the two main categories of PFAAs, and perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) are the primary representatives of PFCAs and PFSAs, respectively. Their good properties have made them common industrial and consumptive products since the 1950s (Renner, 2001), leading to massive distribution of PFAAs not only in air, soil, and water, but also in biota globally (Giesy et al., 2001; Dai et al., 2006; Olsen et al., 2003, 2005).

Over the past few decades, PFAAs have drawn increasing attention from scientists due to their environmental persistency, bioaccumulation, and extensive distribution worldwide. Animal experiments and epidemiological studies have indicated that PFAAs exhibit considerable toxicities, including hepatotoxicity, developmental toxicity, immunotoxicity,

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and glucose homeostasis disorder (Steenland et al., 2010; Lau et al., 2007; Rosen et al., 2013; Halldorsson et al., 2012; Maisonet et al., 2012; Corsini et al., 2014; Nelson et al., 2010; Taylor et al., 2013). The reproductive and developmental toxicities of PFAAs, which can result in broad and varied health consequences in offspring, are of particular concern. A nationwide cohort study in the US suggested an inverse association between maternal plasma PFOA levels and birth weight of newborns (Fei et al., 2007). Similarly, epidemiological studies on human cord blood from mothers found that PFOA was capable of traversing the human placental barrier and exposing the fetus *in utero*, implying a potential developmental toxicity of PFAAs (Apelberg et al., 2007). In addition, PFAAs may serve as endocrine disruptors and cause adverse effects (De Coster and van Larebeke, 2012; White et al., 2011). For example, sperm quality among 105 Danish men from the general population was reportedly diminished in association with more intense exposure to PFOA and PFOS (Joensen et al., 2009). Animal research has also demonstrated that *in utero* exposure to PFOA lowered sperm concentration and total sperm count, and increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Vested et al., 2013).

Although extensive research on potential endocrine disruption and reproductive toxicology has been carried out with PFOA and PFOS, which are both dominant PFAAs in animals and humans, few reports have compared the endocrine disruption abilities among different PFAAs. Given that PFAAs of varying chain length (C4–C14) have been detected in humans, though at lower levels (Olsen et al., 2005), comparative study will be very helpful in clarifying the contribution of different backbone carbon chain lengths and functional groups to toxicity. Mouse Leydig tumor cells (mLTC-1) are commonly used cell line in steroidogenesis related research. To some degree, mLTC-1 can maintain the properties of the original Leydig cell and be responsive under certain stimuli, such as adenosine 3′,5′-cyclic monophosphate (cAMP), LH, and human chorionic gonadotropin (hCG), and are also capable of translating messages for the production of steroids, such as that done by normal Leydig cells (Rebois, 1982). In this study, we investigated the concentration–response

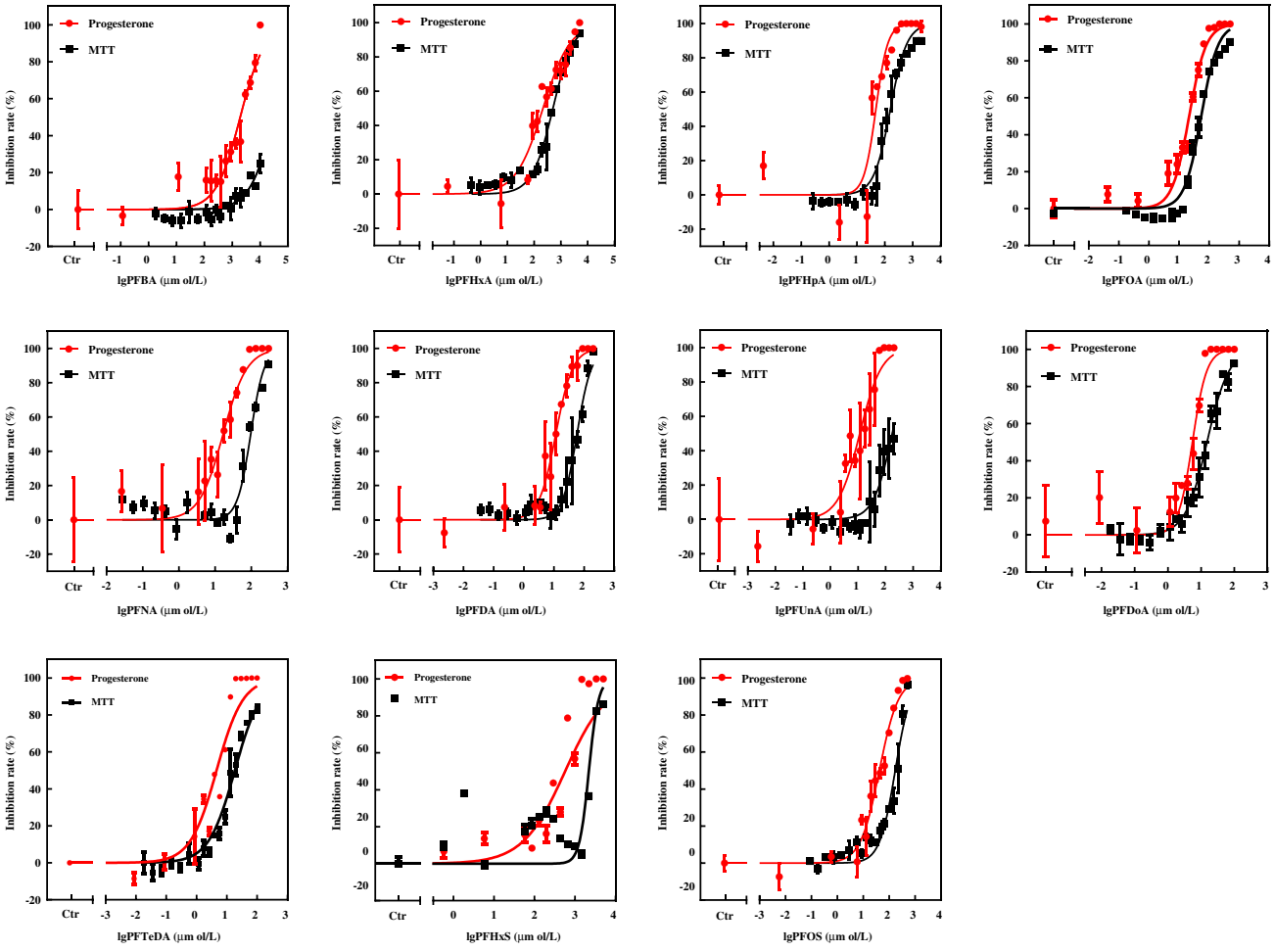

Fig. 1 – S-shape dose–response relationship between inhibition rate of progesterone production (red line and dots), and that of cell activity (black line and squares) and PFAA concentration after mLTC-1 were exposed to eleven individual PFAAs for 24 hr. Results are expressed as mean ± SEM (*n* = 3). Ctr: control; PFAA: perfluoroalkyl acid; mLTC-1: mouse Leydig tumor cells; SEM: standard error of the mean.