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Endocrine disruptors and arterial hypertension: A developing story

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ABSTRACT

Endocrine disrupting Chemicals (EDCs) are substances that interfere with hormones by several mechanisms including receptor activation or antagonism, changes in gene and protein expression, modification of signal transduction, and/or epigenetic modifications in hormone-producing cells. A survey conducted by the European Union in a Northern Italian region led to the discovery of a large environmental contamination of drinking water by perfluoroalkyl substances (PFAS). As the exposed population showed a high prevalence of arterial hypertension and cardiovascular disease, we decided to investigate if PFAS could enhance the biosynthesis of aldosterone. To this aim, we exposed human adrenocortical carcinoma HAC15 cells to PFAS and found that PFAS markedly increased aldosterone synthase (*CYP11B2*) gene expression and aldosterone secretion. Moreover, we found that they promoted reactive oxygen species (ROS) production in mitochondria, the organelles where aldosterone biosynthesis takes place. PFAS also enhanced the effects of the aldosterone secretagogue angiotensin II (Ang II) on *CYP11B2* gene expression and aldosterone secretion. We also found that not only PFAS but also polychlorinated biphenyl 126 (PCB126), a chemical compound belonging to a different category of EDCs, can increase *CYP11B2* gene expression and aldosterone secretion in adrenocortical cells. This novel information needs to be considered in the context of a widespread exposure to the most common EDC, that is excess Na^+ intake, whose detrimental effects on human health occur in the setting of aldosterone production exceeding the physiological needs and lead to high blood pressure, congestion, and cardiovascular and renal damage.

1. Introduction

The endocrine system finely tunes multiple functions in the human body through highly sophisticated mechanisms, which can be deeply influenced by exposure of human beings to an environment densely contaminated by pollutants that affect the function of endocrine glands. To identify natural or man-made chemicals that act as ligands affecting the synthesis, plasma levels, metabolism and/or clearance of hormones and, thereby, their actions, the World Health Organization (WHO) has coined the term endocrine disruptors or endocrine-disrupting chemicals (EDCs) [1,2]. Since EDCs are extensively present in food and contact materials, cosmetics, household goods, and toys, humans are widely exposed to their action [1].

Epidemiological evidence supports an association between EDCs exposure and diminished quality of life, lower cancer-free survival, and endocrine diseases [3], including obesity, type 2 diabetes mellitus, and metabolic syndrome [2,4–6]. Recent data have also highlighted a link between some EDCs and arterial hypertension (HT), the most prevalent cardiovascular risk factor worldwide, which causes millions of events, such as myocardial infarction, stroke, heart failure, chronic kidney disease, and renal artery disease, every year, by interacting with other known cardiovascular risk factors [7].

We will herein examine the evidence linking EDCs to HT with particular focus on the role of perfluoroalkyl substances (PFAS), which

Abbreviations: Ang II, Angiotensin II; *CYP11B2*, Aldosterone synthase; HT, Arterial hypertension; BP, Blood pressure; EDCs, Endocrine disrupting chemicals; PFOA, Pentadecafluorooctanoic acid; PFAS, Perfluoroalkyl substances; PFOS, Perfluorooctanesulfonic acid; PCB126, Polychlorinated biphenyl 126; ROS, Reactive oxygen species; WHO, World Health Organization.

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have been included among the EDCs by the WHO, because of the multiple adverse effects that they exert on health and endocrine system [1,2]. We will also briefly examine the role of polychlorinated biphenyl 126 (PCB126), a chemical compound belonging to a different category of EDCs. The role of these EDCs will be discussed in the context of excess Na^+ intake that, albeit not commonly included among EDCs yet, can also be regarded as an endocrine disruptor because it deeply affects the function of the renin-angiotensin-aldosterone system, the main hormonal system that regulates body fluid volumes and blood pressure (BP), and can interact with PFAS and PCB126 in raising BP.

2. Perfluoroalkyl substances (PFAS)

PFAS are widely used in industrial processes and commercial products due to their water- and oil-repellent properties and chemical and thermal stability [8,9]. Accordingly, they are widely dispersed in the biosphere and, through the ingestion of polluted water or food, they contaminate living organisms, such as fish, birds, mammals, and humans [10,11]. Of much concern, once ingested, PFAS are poorly metabolized and excreted and, therefore, remain for years in blood, tissues, and organs, with an estimated elimination time from human plasma ranging from 5 to 8.5 years [9].

Owing to these features and their multiple detrimental effect on human health, the production of PFAS has been banned in several states of the US, and their production has been relocated to other countries, including Europe where environmental pollution by PFAS has become a major public health issue. For example, in North-Eastern Italy, one major global industrial producer of PFAS, caused a huge environmental pollution because of the spilling of PFAS in a water duct supplying a large portion of the Vicenza province. Accordingly, over a million residents living in the contaminated area, thereafter defined as “Red Zone”, have been exposed to PFAS through drinking tap water for over two decades, until autumn 2013, when an EU initiative discovered and stopped the pollution [12].

At that time, systematic measurements of circulating PFAS plasma levels in inhabitants of the contaminated municipalities allowed to discover that the PFAS with the highest serum concentrations were pentadecafluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) [12,13], whose blood concentrations were, respectively, 8- and 1.5-fold higher than that found in residents of uncontaminated areas [12].

Epidemiological data collected during the period 1980–2013 showed that inhabitants of the Red Zone had higher relative risks of death, diabetes mellitus, cerebrovascular diseases, myocardial infarction, Alzheimer’s and Parkinson’s diseases, kidney, and breast cancer than subjects living in nearby municipalities drinking uncontaminated water, despite similar ethnic background, socio-economic conditions, and smoking habits [14].

A health surveillance program, established to aid in the prevention, early diagnosis and treatment of disorders possibly associated with PFAS exposure [13], also demonstrated that serum PFOA and PFOS levels were directly related to increased systolic and diastolic BP values and to increased prevalence of HT, the latter only in men [15].

The high prevalence of HT in population exposed to PFAS was confirmed in multiple studies in Europe, US, and China. The cross-sectional analysis of data collected from 6,967 adults included in the 2003–2012 surveys of the National Health and Nutrition Examination Surveys (NHANES) confirmed the association of PFAS with the prevalence of HT [16]. In the SWAN Study (Study of Women’s Health Across the Nation), that included 1058 midlife women initially free of HT, PFAS were directly associated with incident HT [17]. Moreover, an increase in circulating PFAS was associated with higher diastolic blood pressure and an increased prevalence of HT in 1,273 healthy Chinese, from the “Isomers of C8 health project”. When stratified by sex, these effects of PFAS on blood pressure and HT were stronger in women [18].

However, other studies reported either no or negative association of PFAS levels with HT or blood pressure [19–21].

Whether the associations between PFAS and BP and HT were just chance findings or had a mechanistic explanation remained unknown and further research are needed to clarify this aspect.

3. Perfluoroalkyl substances (PFAS) as EDCs

In 2013, by studying the effect of PFOA in a human adrenocortical carcinoma cell line H295R Du *et al.* [22] reported that PFOA, at a concentration ranging from 3 nM to 300 nM, altered the expression of major steroidogenic genes, including *StAR*, *17βHSD1*, *CYP19*, *3βHSD2*, and of the steroidogenic factor *SF-1*. Three years later, Kang *et al.* [23] by investigating the effects of PFOA and PFOS on the synthesis of sexual hormones in the same cell line, incidentally observed that PFAS also increased *CYP11B2* and *CYP11B1* mRNA transcription [22], thus suggesting that PFAS could modulate not only the early but also the late steps of the adrenocortical steroidogenesis. These observations provided preliminary evidence for a role of PFAS as potent EDCs but remained serendipitous and furnished information neither on the effect of PFAS on aldosterone release and BP, nor on the mechanisms whereby PFAS can induce aldosterone biosynthesis.

4. Perfluoroalkyl substances (PFAS) and blood pressure

Based on the higher BP and prevalence of HT in the Red Zone population and the aforementioned *in vitro* findings, Caroccia *et al.* hypothesized that PFAS could enhance aldosterone biosynthesis, and thereby raise BP. To challenge this hypothesis, they investigated the effect of the two main PFAS pollutants, PFOA and PFOS, on aldosterone synthase (*CYP11B2*) gene expression, aldosterone secretion, and mitochondrial oxidative stress in human adrenocortical HAC15 cells, a clone derived from H295R cells [24]. Compared to the parental cell line, these cells produce more aldosterone *in vitro* and responde better to Ang II [25]. Moreover, considering that aldosterone biosynthesis requires both the mitochondrial enzyme CYP11B2 and the highly oxidative environment existing in the mitochondria [26], and since PFAS were described to promote generation of reactive oxidative species (ROS) [27], Caroccia *et al.* investigated if PFAS exposure could increase the generation of ROS specifically in the mitochondria using a molecular probe (MitoSOX™ Red) that selectively reveals superoxide levels in the organelle [24].

In brief, their results showed that PFOA and PFOS, at concentration of 1 and 10 μM, which have no effect on adrenocortical cells viability, elicited the following effects: i) they enhanced aldosterone synthase gene expression and aldosterone secretion in a concentration-dependent way (Fig. 1); ii) they had a synergistic effect on the transcription of aldosterone synthase when added simultaneously; iii) they augmented whole-cell and mitochondrial reactive oxygen species production, measured with dihydroethidium (DHE) fluorescent probe and MitoSOX™, respectively; iv) they potentiated the effect of angiotensin II (Ang II), one of the main aldosterone secretagogues. Of further relevance, the effects of PFAS on *CYP11B2* transcription, aldosterone secretion and ROS production were abolished by exposure to the ROS scavenger tempol [24].

Collectively these results support the view that chronic *in vivo* exposure to PFAS upscales the physiological production of aldosterone (Fig. 1, middle panel) and potentiate the effects of known physiologic aldosterone secretagogues, like Ang II, by increasing the production of ROS in the mitochondria of human adrenocortical zona glomerulosa cells.

5. Polychlorinated biphenyl 126 (PCB126)

Polychlorinated biphenyl 126 (PCB126) is a chemical compound belonging to a different category of EDCs. Three different studies by Lih-Ann et al. indicated that at high concentrations PCB126 stimulated basal and inducible aldosterone production concomitantly with activation of

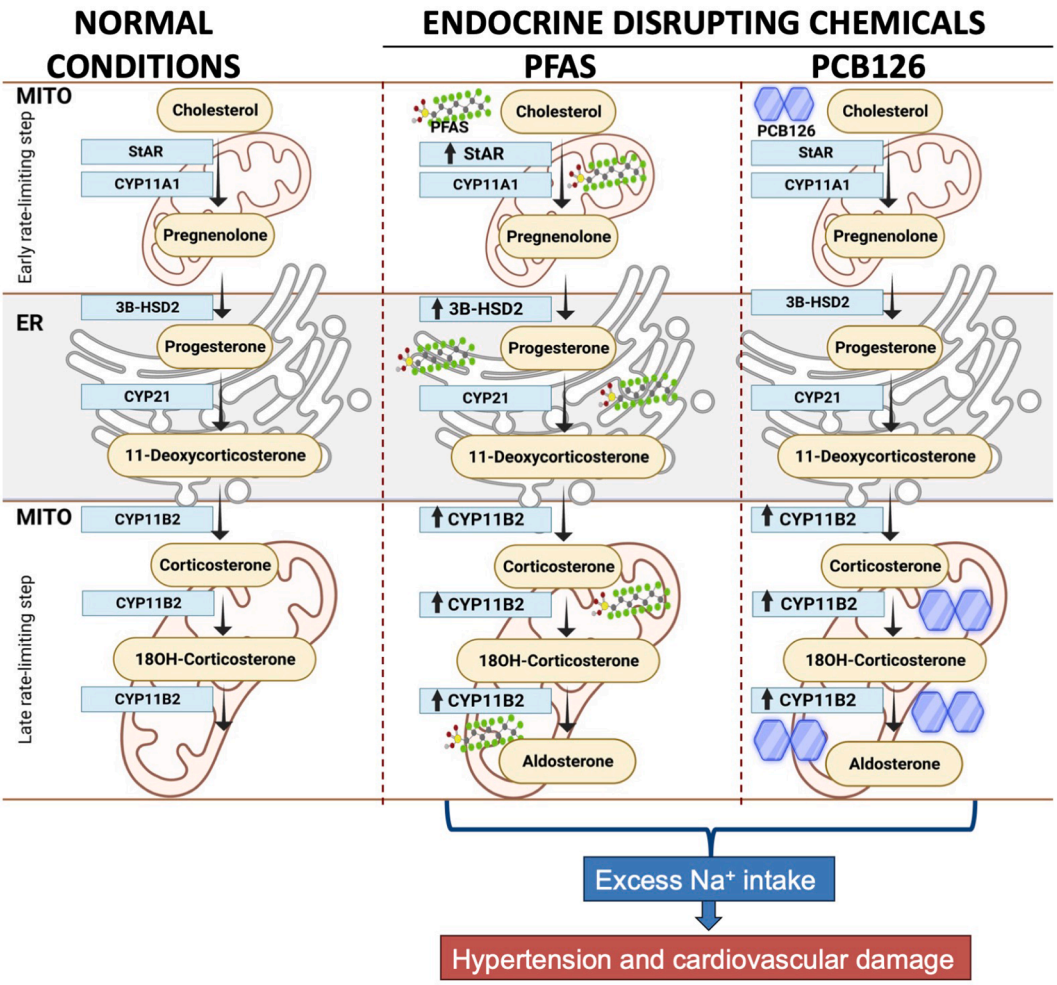

Fig. 1. Physiological pathway of aldosterone production (left) and mechanisms whereby EDCs as PFAS (middle) and PCB126 (right) increase aldosterone production by acting on both the early steps and the late steps of adrenocortical steroidogenesis. In the setting of a widespread exposure to another EDC, *i.e.*, excess Na^+, aldosteronism leads to arterial hypertension and excess cardiovascular damage, ultimately causing cardiovascular and cerebrovascular events. MITO: mitochondria; ER: endoplasmic reticulum; PFAS: perfluoroalkyl substances; PCB126: polychlorinated biphenyl 126.

the *CYP11B2* gene (Fig. 1, right panel) and also elevated transcriptional expression of the type I Ang II receptor (AT1-R), thus sensitizing the cellular Ang II responsiveness in both basal and inducible aldosterone biosynthesis [28]. They also reported that PCB126 up-regulated steroidogenic *CYP11B1* and *CYP11B2* mRNA expression by increasing post-transcriptional mRNA stability [29]. Of interest, potassium and PCB126 synergistically upregulated mRNA expression of both *CYP11B1* (11β-hydroxylase) and *CYP11B2*, whereas PCB126 also appeared to

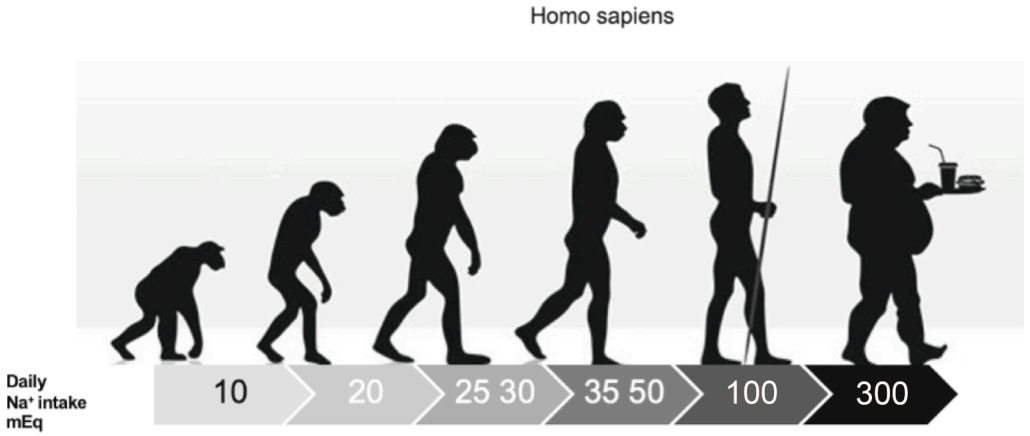

Fig. 2. The cartoon illustrates the average Na^+ intake through evolution from primates, to "collectors and hunters" to the modern sedentary lifestyle. Please note how Na^+ intake has exponentially increased with acquisition of the standing posture, and, moreover, with the modern sedentary lifestyle and consumption of preserved Na^+-rich foods.

regulate these two genes at the post-transcriptional level, indicating that potassium enhanced the potency of PCB126 to induce CYP11B1- and CYP11B2-mediated steroidogenesis [30].

6. Excess Na^+ intake as an EDC

The relevance of these findings needs to be considered in light of the current exposure to excess Na^+ intake as discussed in the next section. In the stone age our ancestors, who were "collectors and hunters" did not have access to salty foods. Hence, to cope with the challenges of dehydration and hypovolemia and survive until the reproductive age, they needed to save the very low salt that they could gather from a diet virtually free of Na^+. Millions of years of evolution helped them to fight these challenges by providing them with a genetic background very effective at preserving salt [31]. As shown in the Fig. 2, because of the generalized use of salt to preserve foods, we are now exposed to an enormous amount of salt, which plays an instrumental role in raising BP. Moreover, unlike calories, our body is unable to store Na^+. Therefore, it reacts to excess salt intake by increasing BP, which furnishes a higher renal perfusion pressure and glomerular filtration rate, thus allowing an increase of urinary Na^+ excretion [32,33]. Salt-senvitivity is by no means a qualitative trait but rather a quantitative continuous trait in the population; however, by using arbitrary cut-offs for classifying subjects into salt-sensitive and salt-resistant, it is generally estimated that up to 20 % of the hypertensive patients do respond to Na^+ restriction and Na^+ loading with a decrease and an increase of BP, respectively [34].

Likely, as mentioned above, this trait is genetically determined. However, environmental factors, like the EDCs described above, by upscaling the production of the Na^+-retaining hormone aldosterone, can also play a role. Hence, according to this view, HT would develop as result of an interaction between excess salt intake and relative hyperaldosteronism, either due to a genetic background and/or to exposure to environmental EDCs, such as PFAS.

7. Discussion

We herein described some EDCs, including PFAS and PCB126, that were recently unambiguously documented to increase aldosterone production in human adrenocortical cells *in vitro*. At concentrations mimicking those found in exposed workers of the polluted Red Zone of Italy, similar to those found in other contaminated areas of West Virginia and Ohio [35], PFOA and PFOS, the two most prevalent PFAS detected in the plasma of the Red Zone population, enhance aldosterone secretion via ROS production and markedly increased *CYP11B2* gene expression and aldosterone release in human adrenocortical HAC15 cells [24].

In line with these observations, polychlorinated biphenyl 126 (PCB126) was also shown to increase *CYP11B2* gene expression and aldosterone secretion, albeit only when used at high concentrations, in adrenocortical cells [29].

These findings highlight an important potential mechanism by which BP and HT are increased in communities exposed to environmental pollution with these agents.

Of note, as the regulation of aldosterone biosynthesis is a highly complex process involving peptide-activated G-protein-coupled receptors and various peptide ligands that act in a concerted way [36,37], establishing that PFAS and PCB126 modulate the action of known physiological stimuli of aldosterone secretion, such as angiotensin II, is a further important piece of knowledge. Both PFOA and PFOS, alone or in combination, markedly potentiated the secretagogue effect of Ang II on aldosterone production [24]. This is quite important as even small increases in the plasma concentrations of aldosterone within the physiologic range were shown to raise blood pressure in the general population of the Framingham Offspring study [38] and to be associated with the two main detrimental consequences of high blood pressure: left ventricular hypertrophy [39] and incident atrial fibrillation in the ARIC study [40]. Importantly, both PFAS and PCB126 were shown to interact with angiotensin II. Therefore, these discoveries may be relevant not just for the exposed population, but also in the population at large, as they might help to explain the apparent epidemics of primary aldosteronism [41,42].

The effect of exposure to EDCs that raise aldosterone secretion also need to be considered in the context of exposure to another, probably the most important EDC, *i.e.,* excessive Na^+ intake, which is a generalized feature of the modern dietary habits in most countries. In fact, the detrimental effects of aldosteronism are markedly blunted or even annulled when Na^+ intake is low, *i.e.,* below 100 mEq/day corresponding to less than 5 g NaCl per day. Unfortunately, this level of sodium intake is less than half the daily consumption of salt in most European countries [43].

In summary, while the importance of PCB126 as environmental contaminant remains uncertain, at least two widely present environmental pollutants, the PFAS, PFOA and PFOS, enlisted among EDCs, act as potent inducers of mitochondrial oxidative stress and aldosterone secretion in human adrenocortical cells.

At this stage available results support the hypothesis that PFAS might act as etiological and/or facilitating factors in hyperaldosteronism, both in the presence (*i.e.*, secondary aldosteronism) and the absence of overt activation of the renin–angiotensin system (*i.e.*, primary aldosteronism). If they can accumulate in adrenal gland and promote the formation of the aldosterone-producing adenoma remains to be investigated.

Of note, based on the association between PFAS exposure and adverse outcomes, in the US some states, such as California, have prohibited their use for goods aimed at children's use. Moreover, some companies making PFAS have voluntarily set out to replace long-chain PFAS with short-chain PFAS in recent years [44]. However, data on the biological activity of the short-chain PFAS and their long-term effects on human health are scant, thus warranting further research.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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