Xenobiotics Modulating Aryl Hydrocarbon Receptor in Energy Homeostasis

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There are fundamental sex differences in the regulation of energy homeostasis. Better understanding of the underlying mechanisms of energy balance that account for this asymmetry will assist in developing sex-specific therapies for sexually dimorphic diseases such as obesity. Multiple organs, including the hypothalamus and adipose tissue, play vital roles in the regulation of energy homeostasis, which are regulated differently in males and females. Various neuronal populations, particularly within the hypothalamus, such as arcuate nucleus (ARC), can sense nutrient content of the body by the help of peripheral hormones such leptin, derived from adipocytes, to regulate energy homeostasis. Substances from diet and environmental contaminants can exert insidious effects on energy metabolism, acting peripherally through the aryl hydrocarbon receptor (AhR). Developmental AhR activation can impart permanent alterations of neuronal development that can manifest a number of sex-specific physiological changes, which sometimes become evident only in adulthood. AhR is being investigated as a potential target for treating obesity. The consensus is that impaired function of the receptor protects from obesity in mice. AhR also modulates sex steroid receptors.

Keywords: aryl hydrocarbon receptor ; energy homeostasis ; xenobiotics ; sex differences

1. Introduction

The fact that industrial chemicals adversely affect human health is not new; environmental contaminants can have a profound, long-lasting impact on numerous disease conditions, including obesity and metabolic dysfunction. The aryl hydrocarbon receptor (AhR) is a principal target for neutralizing a variety of environmental toxicants. Moreover, AhR contributes to several physiological functions in the brain, which includes neuroendocrine functions, neurogenesis, cell differentiation, and cell survival [1]. AhR has been characterized in several animal models [2]. This receptor is present in the cortex, hippocampus, cerebellum, and highly expressed in the hypothalamus when compared to other regions of the brain [3]. AhR is a basic-helix-loop-helix/period-aryl hydrocarbon nuclear translocator-single minded (bHLH/PAS) family of genes, which binds a variety of ligands. bHLH-PAS proteins typically possess two separate PAS domains, PAS-A and PAS-B, composed of 50 amino acid repeats that mediate protein–protein interactions. Homomeric or heterodimeric PAS proteins act as transcription factors, which bind to DNA through the bHLH domain to affect expression of many target genes and numerous physiological functions [4][5][6]. Functions of AhR are influenced by the ligand affinity, heterodimeric partnerships, cell-type, and other environmental factors. Canonical AhR signaling starts from ligand binding which causes the receptor to be translocated inside the nucleus, where it complexes with the AhR nuclear translocator (ARNT) and forms a heterodimer. The heterodimer then binds to the xenobiotic response element (XRE) sequence to regulate transcription of various genes including the cytochrome P450 Cyp1 family, phase II detoxification genes, and numerous others [7], including genes contributing to the endocrine system [7][8]. AhR also interacts with various members of the nuclear receptor superfamily, including receptors for estrogens [9][10][11], androgens [12][13][14][15], glucocorticoids [16], and thyroid hormones [17]. AhR-ER crosstalk was first proposed around four decades ago and is complex. A majority of studies support inhibitory interactions, where activated AhR attenuates the ERα signaling. The precise mechanisms remain equivocal, but some evidence supports metabolism of estrogen via the induction of cytochrome P450 Cyp1 family to increase proteasome-mediated degradation of ERα, and recruitment of ERα by AhR ligands to the AhR bound promoters, reducing the ERα signaling [18]. AhR can also be anti-androgenic, through interference between AhR ligands and transcriptional interference with AR in testosterone signaling pathways [12]. Moreover, AhR is expressed in all cell lineages of pituitary tissues in both mice and humans [19][20][21]. Most works on AhR actions in pituitary have focused on endocrine disruption and xenobiotic effects. It is well accepted that AhR signaling is crucial for sex-steroid biosynthesis during the fetal period, which helps determine sexual dimorphic phenotypes detailed below in the next sub section. In the context of energy homeostasis, pituitary hormones have XRE sequences in their promoters, which indicate that AhR may affect their expression. For example, POMC, which is a precursor protein not only for α-MSH (that regulates appetite) but also for ACTH, has several upstream XRE motifs [22]. GH also possesses XRE sequences in its promoter, for which AhR can

compete to regulate its expression [23][24]. Beta-naphthoflavone (BNF), an agonist of AhR, can disrupt several genes involved in the neuroendocrine regulation of stress [25][26]. Overall, most studies have shown AhR to affect the HPG axis, while the effects on GH, TSH, and ACTH are still not clear [27][28][29][30]. This highlights key discoveries related to AhR influences on the neuroendocrine system to control energy homeostasis and provides rationale for exploiting AhR as a therapeutic target in obesity for both the sexes.

2. AhR in Early Sexual and Neuroendocrine Development

Emerging evidence suggests that early life exposure to environmental toxicants can have long-lasting impacts on development and health. bHLH-PAS family proteins are crucial regulators of the hypothalamus and neuroendocrine development [31][32][33]. As a mediator of toxicity to environmental toxicants, AhR can be activated by numerous exogenous ligands originating in air, earth, water, and living organisms. Most toxic contaminants that are AhR ligands are man-made and are produced by various industries, including pesticide, bleaching, wood preservation, metallurgy, and many more. Furthermore, naturally occurring and endogenous ligands can activate AhR and influence physiological function. Among the man-made ligands that generate major health concerns are halogenated aromatic hydrocarbons, such as polyhalogenated dibenzodioxins, dibenzofurans, biphenyls that bind to AhR with high affinity even in the pico-nanomolar range [34]. Many exogenous AhR ligands such as TCDD and PAHs can cross the blood brain barrier (BBB) to mediate AhR action in the brain. Likewise, many endogenous AhR ligands derived from tryptophan metabolites such as indoxyl-3-sulfate (I3S), indole-3-carbinol (I3C) and FICZ also cross the BBB via gut–brain axis to modulate AhR activity in the brain in response to various environmental and metabolic cues [26][35]. Their ubiquitous distribution, lipid solubility and long-lasting half-life, promote bioaccumulation of the compounds throughout the food chain by depositing in lipid-heavy tissues such as adipose and brain [36][37][38]. There they show immense resistance to breakdown. The Environmental Protection Agency (EPA) has recognized a link between an increased morbidity rate and level of Polychlorinated Biphenyls (PCBs), which also includes dioxins, in the general US population [39]. Alarmingly, people in highly contaminated regions might have surpassed the tolerable dioxin exposure [40]. Moreover, dioxins may accumulate during prenatal and postnatal periods via the placenta and breast milk [41][42][43]. With a half-life that is roughly decades, the chances of staying in tissue from birth to adult to activate AhR chronically are high. Dioxin burdens in the perinatal stage can lead to irreversible changes in brain development that become apparent in adulthood. Therefore, understanding how these toxicants impact development is critical. Reproductive development appears sensitive to toxicant exposure. Prenatal exposure to the potent AhR agonist, TCDD feminizes male rats [39][44][45][46]. TCDD-treated male mice exhibit gonadotropin secretion patterns similar to females, and decreased plasma androgen levels [45]. Feminization of the preoptic area of the hypothalamus may contribute to this feminization [47]. Prenatal exposure to TCDD in females leads to reproductive dysfunction in adulthood, including complications in estrus cycle, ability to achieve and maintain pregnancy, and sometimes infertility [44][48][49]. Altered gonadotropin release patterns due to TCDD-induced alterations of the POA is considered to be the reason for diminished reproductive capacity.

The link between AhR and sex steroid receptor pathways prompted exploration of AhR expression in known sexually dimorphic areas of the brain. Interestingly, AhR and ARNT expression is sexually dimorphic in the hypothalamus, particularly in the POA, which is important for sex behaviors [50][51]. Overlap with regions high in ER [52] may explain why the alteration of gonadal hormones due to TCDD exposure leads to sexual dimorphism. Similarly, interaction between AhR and ER may affect function of other hypothalamic nuclei, including the anteroventral periventricular (AVPV), arcuate (ARC), and ventromedial (VMH). Interestingly, these regions regulate both sexual behavior and energy homeostasis [53][54][55][56]. Manipulation of sex hormones, and their receptors during development can lead to permanent changes in neuronal connectivity and functions, and exogenous AhR ligands may affect perinatal neuronal development, which can be irreversible. Therefore, it is very important to understand the molecular mechanisms related to AhR action in the developing brain to evaluate the possible impact on human health.

3. AhR Contribution to Energy Metabolism and Obesity

Toxicological studies on AhR led to the hypothesis that AhR might regulate energy balance [57]. Among many symptoms, TCDD toxicity in humans causes anorexia and weight loss [57]. Targeted studies revealed that AhR can modulate metabolically important gene expression, including regulation of blood glucose, lipid, and energy homeostasis [58][59][60][61]. Initial studies in mice deficient in AhR directed a focus on metabolism due to developmental defects involving liver and other metabolically important organs. However, the first evidence of AhR regulation of energy metabolism appeared a decade ago [62][63]. Lee et al. demonstrated that activation of AhR has the potential to cause fatty liver disease/hepatic steatosis through altered fatty acid transport inside liver, and increased lipid spillover from fat depots. The lab demonstrated a direct connection between AhR deficiency and peroxisome proliferator-activated receptor alpha (PPARα)

loss of function in liver to hinder glucose and fatty acid metabolism. It is now well established that AhR deficiency protects mice from high-fat diet (HFD)-induced obesity [64][65]. Under HFD, tryptophan metabolites that act as AhR ligands are increased, which activate AhR and promote an obese phenotype [66]. WAT is critical for metabolism of kynurenine (Kyn), a downstream catabolite of Trp; HFD increases circulating Kyn in obese individuals [67]. Exhaustion of Trp inhibits the production of other Trp metabolites such as serotonin, which is involved in satiety. Moreover, excessive Kyn promotes AhR activity to activate the AhR/Stat3/IL-6 pathway in adipocytes and mediates the development of obesity and insulin resistance [68]. The lab found that HFD alters many key hepatic and adipose genes, including fat synthesis, accumulation, and catabolism pathways, which contribute to dietary obesity and insulin resistance. Moreover, AhR deficiency protects against HFD-induced elevations in leptin and insulin, and reductions in adiponectin, which are all indicators of metabolic dysfunction. An increase in energy expenditure in AhR-deficient mice, associated with enhanced expression of uncoupling protein 1 (UCP1) contributes to metabolic protection in these mice. Furthermore, mice with a low affinity form of AhR (B6.D2) are also protected from diet-induced obesity [64]. A variety of nuclear receptors (such as genes from the PPAR family) were important for fat biogenesis, accumulation and mobilization are altered in these animals. Together, this indicates that reduced AhR function provides mice with mechanisms that maintain healthy energy balance in the face of HFD.

AhR can also regulate fibroblast growth factor 21 (FGF21), which protects properties against metabolic disease by promoting energy expenditure and improving both lipid and glucose metabolism [69][70]. Produced by the liver, circulating FGF21 acts on adipocytes to promote thermogenesis, insulin sensitivity and produce a favorable lipid profile [71][72][73]. FGF21 can also be released from adipose tissue to act in an autocrine or paracrine fashion to increase thermogenesis [72][73][74][75]. FGF21 promotes BAT thermogenesis and differentiation of WAT to produce increased numbers of *brite* adipocytes (also known as browning of adipose tissue), through induction of PPARγ [76][77]. *Brite* or *beige* adipocytes express UCP1 and have brown adipocyte-like function [78]. Dense caloric intake stimulates FGF21 expression through a PPARγ in an attempt to improve insulin sensitivity and adipocyte function [79]. Noradrenaline is a potent activator of UCP1 expression and induces '*browning*' of WAT [80]. FGF21 expression is also increased in WAT and BAT after physical activity or cold exposure, and its release has been correlated with release of noradrenaline from activation of SNS [77][81][82][83][84]. There is clear evidence that AhR regulates FGF21 expression, through XRE regions in the FGF21 promoter. Whether AhR up-regulates or down-regulates FGF21 gene expression remains equivocal, with data to support each effect. Some labs found AhR activation suppresses FGF21, and liver-specific deletion induces its expression in mice [85]. However, other studies indicate TCDD activation of AhR promotes hepatic FGF21 expression [86]. Differences in the duration of AhR activation may reconcile the disparate results. Acute induction of FGF21 by short-term AhR activation might be beneficial, whereas long standing AhR activity may have opposing effects, including development of FGF21 resistance. The developmental stage of AhR deletion may also complicate the issue. Postnatal deletion of hepatic AhR may affect weight loss through increase in adipose-regulated increases in energy expenditure [87]. Protection of mice bearing a constitutively active form of AhR from diet-induced obesity and diabetes is abolished upon FGF21 knockdown [88]. In summary, although the exact consequences of AhR-FGF21 interactions remain unclear, AhR seems to use both the FGF21 and PPAR family to modulate lipid and energy metabolism.

4. Sex-Specific AhR Modulation of Energy Balance

Obesity and its associated diseases, such as diabetes, can develop through sex-specific mechanisms manifested by dissimilar gene expressions in metabolic tissues [89]. AhR affects energy homeostasis and gene expression patterns in many metabolic tissues including adipose tissue, liver, and brain, which also display differences between sexes. AhR contributes to sex-specific differences in a complex manner. Effects of AhR deletion appear obfuscated by the timing of AhR deletion. For example, in liver, conditional knockout during gestation shows different effects [90]. Specific gestational deletion of AhR from liver exacerbates metabolic disease conditions, such as hepatic steatosis, under HFD, whereas CKO from adult liver helps ameliorate the pathology [87][90]. Molecular studies substantiate these findings, where HFD treatment of animals with gestational excision showed augmented or unchanged gene expression related to various metabolic processes; there was an increase in lipogenesis and inflammation, and no differences in fatty acid uptake, β-oxidation, or gluconeogenesis. On the other hand, adult CKO of AhR from liver demonstrated significantly less weight gain and adiposity from HFD. These animals had increased respiratory capacity of BAT and WAT, due to more production of FGF21 by the liver. The lab obtained similar results in an adipose-specific adult CKO (Haque and Tischkau, unpublished results) mouse compared to gestational adipose-specific AhR CKO [91]. Gestational AhR deletion from WAT exhibited increased weight gain, adiposity, inflammation, and significant impairment in glucose homeostasis when fed HFD [91]. In contrast, adult AhR CKO from all types of adipose tissue protected males and females gained significantly less weight and were protected from hepatic steatosis when fed HFD. Effects of adult CKO were more profound in females. Female AhR CKO mice gain metabolic protection from FGF21, PPARγ, and ERα pathways. Increased *beiging* of WAT, adipogenesis, and

decreased VAT are more dominant in females. It appears that AhR-specific adipose deletion protects females from leptin resistance and males from insulin resistance. Although leptin and insulin are satiety hormones, leptin modulates satiety through numerous pathways, and has more robust effects compared to insulin. Leptin can also be modulated by sex steroids; estrogens enhance leptin sensitivity, whereas testosterone induces leptin resistance [92][93]. Moreover, female brains are more sensitive to leptin, whereas males are more reliant on insulin. The effects on leptin and insulin necessitate a better look at sex-specific control of feeding at the central level. Unfortunately, there are currently no available data on hypothalamic effects of AhR loss in energy balance. Both sexes express significant levels of AhR in the hypothalamic arcuate nucleus [1][47]. These studies are necessary to understand the role of AHR in regulating whole body energy metabolism.

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