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Cross-species physiological interactions of endocrine disrupting chemicals with the circadian clock

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Abstract

Endocrine disrupting chemicals (EDCs) are endocrine-active chemical pollutants that disrupt reproductive, neuroendocrine, cardiovascular and metabolic health across species. The circadian clock is a transcriptional oscillator responsible for entraining 24-hour rhythms of physiology, behavior and metabolism. Extensive bidirectional cross talk exists between circadian and endocrine systems and circadian rhythmicity is present at all levels of endocrine control, from synthesis and release of hormones, to sensitivity of target tissues to hormone action. In mammals, a range of hormones directly alter clock gene expression and circadian physiology via nuclear receptor (NR) binding and subsequent genomic action, modulating physiological processes such as nutrient and energy metabolism, stress response, reproductive physiology and circadian behavioral rhythms. The potential for EDCs to perturb circadian clocks or circadian-driven physiology is not well characterized. For this reason, we explore evidence for parallel endocrine and circadian disruption following EDC exposure across species. In the reviewed studies, EDCs dysregulated core clock and circadian rhythm network gene expression in brain and peripheral organs, and altered circadian reproductive, behavioral and metabolic rhythms. Circadian impacts occurred in parallel to endocrine and metabolic alterations such as impaired fertility and dysregulated metabolic and energetic homeostasis. Further research is warranted to understand the nature of interaction between circadian and endocrine systems in mediating physiological effects of EDC exposure at environmental levels.

Keywords

Endocrine disruption; circadian clock; nuclear receptor signaling; reproductive physiology; behavioral physiology; metabolic disruption

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1. Introduction

Endocrine disrupting chemicals (EDCs) are endocrine-active chemical pollutants that disrupt reproductive, neuroendocrine, cardiovascular and metabolic health across species (Gore et al., 2015). EDC exposure during embryonic and fetal development can result in severe impacts on growth and physiology; responses are frequently sexually dimorphic and may be mediated via epigenetic mechanisms (Xin et al., 2015). EDC exposure has additionally been linked to development of hormonal cancers (Gore et al., 2015). Classes of EDCs include polyhalogenated and phenolic compounds, phthalates, pesticides, steroid hormones, pharmaceuticals and personal care products (Wee and Aris, 2017). EDCs enter the environment through industrial, municipal and agricultural runoff as well as consumer product use and subsequent entry into wastewater, and environmental exposures present health threats to humans, wildlife and aquatic organisms (Kabir et al., 2015).

The circadian clock is a light-driven transcriptional oscillator responsible for entraining 24-hour rhythms of physiology, behavior and metabolism (Bass and Lazar, 2016; Malik et al., 2020). The molecular architecture of the circadian clock was first discovered in *Drosophila*, and was subsequently discovered to be highly conserved across species (Wager-Smith and Kay, 2000). Across species, the core clock consists of an activator arm driving transcription of negative clock elements and clock-controlled genes, and repressor arms, which confer a time delay to clock-driven transcription and physiology (Bhadra et al., 2017). In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus is the central pacemaker for the body, which directly responds to light input from the retina (Takahashi, 2016). The SCN generates physiological rhythms of sleep, rest / activity, core body temperature, metabolism and neuroendocrine function, among other systemic processes. The molecular clock is present in most cells of the body, and organ-level peripheral oscillators are entrained by autonomic innervation, hormonal action (eg. glucocorticoids) and other synchronizing signals (zeitgebers) such as feeding / fasting rhythms (Dibner et al., 2010). Clocks present across organisms orchestrate hourly, daily, weekly, monthly and seasonal rhythms in physiology (Lincoln et al., 2003). In teleost fish, peripheral tissues are directly entrainable by light, though some regions of the hypothalamus contain pacemaker neurons as well (Frøland Steindal and Whitmore, 2019; Moore and Whitmore, 2014; Watanabe et al., 2012). Genome duplication events during evolution led to multiple copies of many of the core clock proteins, lending a greater degree of biological redundancy to the teleost molecular clock (Toloza-Villalobos et al., 2015). The circadian system is a critical mediator of physiological processes at all life stages, and disrupted clock function leads to a variety of pathologies such as sleep disorders, depression, chronic stress, cancer, and metabolic disease (Bass and Lazar, 2016).

1.1 Bidirectional crosstalk between circadian and endocrine systems

Extensive bidirectional crosstalk exists between circadian and endocrine systems, and circadian regulation of the major endocrine axes has been recently reviewed. (Neumann et al., 2019). Circadian rhythmicity is present at all levels of endocrine control, from synthesis and release of hormones, to sensitivity of target tissues to hormone action (Neumann et al., 2019). Rhythms of endocrine factors can be short term (hourly and daily) or longer term

(monthly and seasonal) and are strongly sexually dimorphic (Bailey and Silver, 2014). Master pacemaker as well as endocrine organ clocks drive rhythmic endocrine physiology and endocrine organ clocks have been extensively characterized in mammalian systems, for example in pituitary (Lin et al., 2015), pineal gland (Borjigin et al., 2012), pancreas (Perelis et al., 2016), adrenal (Leliavski et al., 2015), liver (Zwighaft et al., 2016), adipose (Froy and Garaulet, 2018) and gonad (Baburski et al., 2019; Sellix, 2015). Rhythmic endocrine physiology is observed across species and has a seasonal component as well, with seasonal variation observed in reproduction, growth and metabolism and locomotor activity rhythms (Cowan et al., 2017; Gómez-Milán and Lozano, 2007; Marchant and Peter, 1986; Nakane and Yoshimura, 2019; Yokota and Oishi, 1992).

Perturbation of circadian systems can lead to a range of endocrine pathologies as summarized for human populations in Table 1. Perturbed reproductive physiology as well as impaired fertility has been documented in female shift workers, and genetic variation in circadian genes *bmal1* and *npas2* was found to be associated with fertility outcomes (number of pregnancies and miscarriage rate) in a cohort study conducted in Finland (Table 1). Shift work is associated with breast cancer incidence in human epidemiology studies, and similarly, circadian gene variance has been found to modify breast cancer risk, as well as breast cancer prognosis and survival in human populations (Table 1). Epidemiological evidence links shift work with a range of metabolic pathologies including diabetes mellitus, impaired energy handling, body mass index and lipid alterations, and metabolic syndrome (Table 1). Further insight into endocrine and metabolic dysregulation following circadian disruption has been demonstrated in core clock gene ablation studies conducted in mice, as outlined in Table 2. Parallel to human epidemiological evidence, altered reproductive physiology and fertility are observed in mouse models following core clock gene ablation systemically or specifically in pituitary or gonad (Table 2). Reproductive physiological perturbations include estrous cycle alterations, impaired fertility and fecundity and impaired gonadal steroidogenesis (Table 2). In the hypothalamic – pituitary – adrenal axis (HPA), systemic or adrenal-specific core clock gene ablation alters rhythmicity of steroid production, impairs adrenal responsiveness to ACTH, impacts behavior and perturbs stress response in a sexually-dimorphic manner (Table 2). Core clock gene ablation similarly causes extensive perturbation of metabolic health and energy homeostasis, leading to alterations in glucose homeostasis and insulin sensitivity, pancreatic dysfunction, altered lipid profiles, obesity and altered feeding rhythms following systemic as well as liver, pancreas or adipose-specific gene ablation (Table 2).

1.2 Nuclear receptor signaling modulates circadian physiology

EDCs perturb endocrine physiology in part through binding a range of nuclear receptors (Bainy, 2007; Casals-Casas and Desvergne, 2011). Nuclear receptor expression is clock-driven and rhythmic, therefore EDC action through nuclear receptor binding has a temporal component which is not well-characterized (Teboul et al., 2008; Yang et al., 2006). Molecular crosstalk between ligand-occupied nuclear receptors and core clock proteins has been observed in mammalian systems, and are summarized in Table 3. REV-ERB α/β and retinoic acid-related orphan receptor (ROR) α/β/γ are nuclear receptors that form a secondary feedback loop with the core molecular clock and directly modulate *bmal1*

transcription (Guillaumond et al., 2005). Core clock repressors *Cry1* and *Cry2* interact with a range of nuclear receptors, including steroid hormone receptors, peroxisome proliferator-activated receptors (PPARs) and xenobiotic sensing receptors PXR and CAR (Kriebs et al., 2017). Glucocorticoids are well-known zeitgebers, capable of synchronizing the molecular clock in the brain and in peripheral tissues, and function to modulate a range of physiological processes such as stress response, energy metabolism, cardiovascular and immune function and cognition (Oster et al., 2016). Direct interaction and transcriptional feedback between the glucocorticoid receptor (GR) and components of the circadian clock has been documented in mammalian systems, and is outlined in Table 3. Peroxisome proliferator-activated receptors (PPARs) are nutrient and metabolite sensing nuclear receptors which function to integrate circadian rhythms with metabolic outputs (Charoensuksai and Xu, 2010). PPARα and γ directly modulate *bmal1* transcription and the PPARα/RXRα heterodimer was found to modulate *Clock*/*Bmal1*-mediated transcription of period and cryptochrome genes (Canaple et al., 2006; K. Nakamura et al., 2008; Wang et al., 2008). In vascular cells, retinoic acid-bound RARα and RXRα interacted with *Clock* and *Mop4* and functioned as a negative regulator of *Clock*/*Mop4*:*Bmal1* transcriptional activity (McNamara et al., 2001). Retinoic acids were also found to upregulate *per1*, *per2* and PPARα expression in an E-box dependent manner (Shirai et al., 2006).

A range of interactions between sex steroid receptors and the molecular clock have been documented. Estrogen and androgen signaling in the SCN modulates responses to photic input (Abizaid et al., 2004; Butler et al., 2012; Karatsoreos et al., 2011) and programs circadian behavioral patterns (Butler et al., 2012; Juárez-Tapia and Miranda-Anaya, 2017; Model et al., 2015; Royston et al., 2016). Estrogens modulate core clock gene expression in the SCN and in peripheral organs (Nakamura et al., 2005, 2001; T. J. Nakamura et al., 2008) and androgens modulate light-induced *Per2* expression in the SCN (Karatsoreos et al., 2011). Progesterone, via the progesterone receptor (PR) modulates the circadian clock in the mammalian uterus (Rubel et al., 2012; Y. Zhang et al., 2019) and estrogen-related receptor α (ERRα) was found to modulate diurnal expression pattern of several core clock genes in mouse liver (Dufour et al., 2011). Figure 1 depicts an overview of circadian aspects of nuclear receptor biology, and Table 3 and Figure 2 summarize documented molecular crosstalk between ligand-occupied nuclear receptors and core clock proteins in mammalian systems.

1.3 Does exposure to endocrine disrupting chemicals alter circadian clock function?

EDCs are defined by the Endocrine Society as: “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action” (Zoeller et al., 2012). As documented above, circadian rhythmicity is innate to endocrine function, bidirectional crosstalk occurs between circadian and endocrine systems, and hormones exert feedback on both peripheral as well as central oscillators through nuclear receptor binding (Table 3). It is plausible that in mimicking or disrupting hormone action, EDCs could similarly alter circadian oscillators themselves or rhythmic physiology. Clear mechanistic evidence demonstrating clock disruption by EDCs does not exist to date, but there are a range of studies demonstrating alterations in core clock gene expression, circadian transcriptional rhythms and rhythmic endocrine physiology following EDC exposure. This review will

explore the evidence for parallel endocrine and circadian disruption following EDC exposure across species. Following a survey of the literature, parallel circadian and endocrine perturbations were identified in a range of species of teleost fish and in rodents. No studies were identified demonstrating parallel endocrine and circadian impacts in amphibian or reptilian species, but adverse impacts of EDCs on reproduction and development have been documented in these organisms as well as invertebrates (Kanda, 2019). In humans, circadian disruption via shift work is associated with a range of endocrine and metabolic pathologies, as outlined in Table 1, and one study explored the association between clock gene polymorphism and cadmium exposure in the context of thyroid cancer risk and severity (Q. Zhang et al., 2019) (Table 1). The studies identified fall into three major categories: circadian gene transcription and rhythmic physiology in the reproductive axis, altered locomotor or behavioral rhythms and altered metabolic homeostasis. In exploring the evidence, we will indicate when studies were circadian in design (conducted under constant conditions) and thus more adequately designed to assess EDC impacts on rhythmic physiology. Direct evidence presented in this manuscript is additionally summarized in Table 4, sorted by EDC class.

2. Clock gene expression and rhythmic physiology in the HPG(L)axis

2.1 Circadian clocks modulate reproductive rhythms

EDCs have been extensively characterized for their impact on reproductive function (Gore et al., 2015; Hachfi et al., 2012). Reproductive function is driven by hourly, daily, weekly, monthly and seasonal rhythms of hormone production and action in the hypothalamus – pituitary – gonad (HPG) axis of mammals, and the hypothalamus – pituitary – gonad – liver (HPGL) axis of oviparous organisms, with the liver contributing proteins necessary for oocyte growth and development (de la Iglesia and Schwartz, 2006; Rosa et al., 2016). In the reproductive axis, the pituitary clock and clocks inherent to gonadotropic cells drive rhythmic hormone production and release in the reproductive axis (Hickok and Tischkau, 2010; Lin et al., 2015). Gonadotropins themselves function as zeitgebers in gonadal clocks. Luteinizing hormone (LH) induces clock gene expression during follicle development in rat ovary and on the day of pro-estrous; in males, LH synchronizes the leydig cell clock and contributes to rhythmicity of testosterone production (Baburski et al., 2019; Gräs et al., 2012; Karman and Tischkau, 2006). Gonadal steroids in turn exert feedback on brain, liver and reproductive organ clocks (Karatsoreos et al., 2011; Nakamura et al., 2010, 2005; Y. Zhang et al., 2019) and Table 3. In zebrafish, rhythmic expression patterns of genes involved in steroidogenesis, gonadal function and sex ratio control were observed in brain and gonad (Rosa et al., 2016). Rhythmic reproductive physiology can be driven by endogenous circadian clocks as well as external zeitgebers such as feeding rhythm and thermocycles (Hontela and Peter, 1983; Weber and Spieler, 1987).

Mouse genetics studies reveal a range of impairments in reproductive physiology and fertility following core clock gene ablation (Table 2). Physiological perturbations include altered estrous cycle, impaired timing of LH and FSH pro-estrous surge and disrupted ovulation in females, and impaired gonadal steroidogenesis in both males and females (Table 2). Both male and female infertility are observed following core clock gene ablation

as well as impaired oocyte fertilization rate, embryo implantation failure, and increased rate of full term pregnancy failure (Table 2). Ablation of *Clock* was additionally found to disrupt nursing and maternal behavior in dams, as well as growth and survival rate of pups (Table 2). Environmental perturbation of circadian function via shift work in humans is associated with altered ovarian cycle pattern, endometriosis risk and prolonged wait time to pregnancy (Table 1). Impaired LH surge, reduced fertility and an increase in adverse pregnancy outcomes has been reported in rodent models of simulated shift work (Bahougne et al., 2020; Summa et al., 2012). Short photoperiod disrupted FSH and prolactin secretion in male hamsters, and led to impaired testicular steroidogenesis, and sleep fragmentation disrupted nocturnal testosterone rhythm in normal men (Chandrashekar and Bartke, 1989; Luboshitzky et al., 2001).

Reproduction is a seasonal event in many vertebrate species, and seasonal reproductive cycles are modulated in part by the circadian clock sensing and responding to changing photoperiod (Nakane and Yoshimura, 2019; D. Zhang et al., 2009). In addition to photoperiod, annual fluctuation in water temperature and lunar periodicity contribute to timing of seasonal reproductive cycles in fish (Ikegami et al., 2014; Oliveira et al., 2009). Endogenous reproductive behaviors are a critical component of reproductive success. EDCs have been characterized to disrupt social dominance hierarchies, sexual selection and courtship behaviors in fish (Coe et al., 2008; Colman et al., 2009; Söffker and Tyler, 2012). Some evidence exists for circadian control of reproductive behaviors. In midshipman fish, circadian rhythm and melatonin control timing of nocturnal courtship vocalization (Feng and Bass, 2016; Rubow and Bass, 2009) and egg laying and courtship behaviors were found to entrain to the light-dark cycle (Weber and Spieler, 1987).

Short-term (pulsatile) through longer-term (seasonal) rhythmicity is inherent to reproductive function across species. Central and peripheral timing signals are critical for rhythms of gonadotropin synthesis and release, gonadal steroidogenesis and estrous cycle patterns. Environmental perturbation of circadian clock function via shift work or altered photoperiod disrupts rhythmic reproductive physiology and leads to fertility impairments. In parallel, EDC exposure is extensively linked to adverse reproductive outcomes (Gore et al., 2015; Hachfi et al., 2012). Given the interconnected nature of circadian and hormonal timing signals in the reproductive axis, it is interesting to explore whether reproductive impairments induced by EDC exposure are due in part to altered clock function or perturbed physiological rhythms. In this section, we will explore evidence for parallel circadian and endocrine impacts following EDC exposure in the reproductive axis.

2.2 Parallel circadian and endocrine impacts of EDCs in the reproductive axis

Altered core clock and circadian rhythm network gene expression has been demonstrated in zebrafish models following exposure to a range of environmental steroid hormones. Natural and synthetic progestins disrupted clock gene expression in brain, and to a lesser extent ovary, of adult zebrafish, with corresponding impacts on gonadotropin expression and gonadotropin regulation pathways (Zhao et al., 2015a, 2015b; Zucchi et al., 2014, 2013). High dose progestin exposure decreased fecundity in adult zebrafish, and a network correlation analysis indicated a significant relationship between the circadian rhythm gene

network and regulation of genes in the HPGL axis (Zhao et al., 2015a). Effects were observed across generations, with perturbations of clock gene expression in F1 generation offspring as well as directly exposed eleuthero embryos (Liang et al., 2019; Zhao et al., 2015a, 2015b). Progestins additionally altered circadian rhythm network gene transcription and increased photo-transduction signals in eyes of adult male and female zebrafish (Zhao and Fent, 2016). Across generations, exposure to natural and synthetic steroid hormone mixtures (progesterone and drospirenone; medroxyprogesterone acetate and dydrogesterone; ethinylestradiol and norgestrel; and to a lesser extent progesterone and estradiol) impacted clock gene expression more strongly than exposure to the individual compounds (Liang et al., 2019, 2017; Zhao et al., 2015b; Zucchi et al., 2014). Exposure to the corticosteroid fludrocortisone acetate altered circadian rhythm, glucose homeostasis and immune response gene networks across generations in zebrafish (Zhao et al., 2016). The circadian clock gene network was among the most significantly altered gene networks in pituitary of juvenile female coho salmon following exposure to 17α-ethynylestradiol, with corresponding pathway impacts observed on gonadotropin regulation, calcium signaling and lipid metabolism (Harding et al., 2013).

In a circadian time course analysis, Zhao et al. (2018) examined the effect of a range of environmental steroid hormones on clock gene rhythmicity in zebrafish eleuthero embryos under constant darkness conditions. Progestins and corticosteroids induced similar transcriptional alterations of clock gene expression, which differed from that of estrogens. Exposure did not abolish transcript cycling, but revealed clock time (CT) 18 to be a sensitive time point for altered clock gene expression. Among the 18 circadian rhythm network genes analyzed by quantitative real time PCR, *per1a* and *nr1d2a* were the most strongly dysregulated genes following a range of steroid hormone exposures. Progestin and corticosteroid-induced impacts on *per1a* and *nr1d2a* expression were recovered using the progesterone receptor (PR) / glucocorticoid receptor (GR) antagonist mifepristone, indicating a role for activated PR / GR in regulating clock gene expression (Zhao et al., 2018). Estrogen-mediated impacts on clock gene cycling were not recovered with tamoxifen, but as this is a selective estrogen receptor modulator, rather than a pure antagonist, the role of estrogen receptor (ER) signaling in altered clock gene expression in this model remains unclear (Xia et al., 2016).

Perturbed circadian transcriptional rhythm has been observed in the HPGL axis in teleost fish following exposure to other EDCs. Bisphenol A perturbed transcriptional rhythm of core clock genes in liver of juvenile mangrove killfish. 17β-estradiol, 4-tert-octylphenol and bisphenol A downregulated *Km-clock* expression in pituitary / brain, muscle and skin of adult hermaphrodite and secondary male fish, with no effect observed in gonad or liver (Rhee et al., 2014). Altered clock gene expression, analyzed at a single time point, and reproductive impairment was observed in fathead minnow following exposure to pulp and paper mill effluents from five different sources (Popesku et al., 2010). Additional impacts on circadian gene transcription in the HPGL axis of teleost fish have been reported following exposure to bisphenol A and cyanotoxins (Choi et al., 2018; Faltermann et al., 2014; Qiao et al., 2016), and lead was found to alter circadian variation of brain neurotransmitters in fathead minnow (Spieler et al., 1995).

In rodent models, EDCs similarly perturbed clock gene expression and rhythmic HPG axis physiology. Walker et al. (2014) examined gene expression in two regions of the hypothalamus known to regulate reproductive function: the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC) following gestational exposure to estrogenic EDCs in Sprague-Dawley rats. Exposure to the industrial PCB mix Aroclor 1221 resulted in delayed timing of eye opening in females and delayed timing of puberty in males, and estradiol benzoate exposure disrupted the estrous cycle in females. Sexually dimorphic impacts on AVPV and ARC gene expression were observed following gestational exposure to estrogenic EDCs. Females exhibited a masculinized expression profile in the AVPV region following A1221 and EB exposure, and exposure resulted in upregulation of two clock genes – *bmal1* and *per2*. Gene expression changes in the ARC were observed to a greater extent in males, with androgen receptor and leptin receptor identified as two candidate genes possibly related to the delayed onset of puberty in males following A1221 exposure (Walker et al., 2014). In golden hamster, exposure to the pharmaceutical triazolam altered circadian rhythm of pituitary LH release (Turek, 1988). The heavy metal cadmium altered rhythmic transcription and physiology in rodent pituitary. In male Wistar rats, low dose cadmium exposure disrupted rhythmic expression pattern of core clock genes in anterior pituitary, altered transcriptional rhythm of redox enzyme expression, and altered daily pattern of secreted prolactin, luteinizing hormone, thyrotropin and corticosterone (Jiménez-Ortega et al., 2012). In two additional reports, cadmium exposure resulted in a disrupted 24-hour pituitary secretion pattern of adrenocorticotropic hormone, growth hormone and thyrotropin, and disrupted the daily pattern of pituitary glutamine, glutamate and aspartate content (Caride et al., 2010b, 2010a).

In summary, a variety of EDCs perturb clock gene expression or rhythmic physiology in the HPG(L) axis across organisms and across life stages, with circadian rhythm network frequently reported to be among the most significantly perturbed pathways following exposure. Environmental steroid hormone exposure is particularly important to investigate in aquatic organisms, and provides a useful model for investigating cross talk of activated nuclear receptors with clock proteins (Rubel et al., 2012; Zhao et al., 2018). Evidence presented demonstrates circadian redox oscillations to be a target of exposure to the heavy metal cadmium (Jiménez-Ortega et al., 2012), and analysis of specific brain regions of the hypothalamus shed light on sexually dimorphic gene expression following EDC exposure (Walker et al., 2014).

3. Hypothalamic – pituitary – thyroid axis and thermoregulation

The hypothalamic – pituitary – thyroid axis is important for energy balance and homeostatic systems such as thermoregulation. Core body temperature exhibits circadian oscillation, and temperature rhythms contribute to entrainment of peripheral tissue clocks (Brown et al., 2002; Morf and Schibler, 2013). A range of EDCs have been demonstrated to impact thyroid axis physiology (Duntas, 2015). Evidence of perturbations in rhythmic thyroid physiology is scarce, but some indication of disrupted circadian temperature rhythm is present in rodent models following EDC exposure. In Long-Evans rats, perinatal exposure to the anti-thyroid drug propylthiouracil (PTU) resulted in a permanently altered core temperature in adult male offspring. Non-monotonic impacts on daily temperature rhythm were present over a range of

doses, with a reduction in mean core temperature of 0.4 degrees C at the highest dose (Johnstone et al., 2013). Additionally, dioxin perturbed circadian temperature rhythm in Long Evans rats and in golden hamsters (Gordon et al., 1996; Gordon and Miller, 1998).

4. Circadian activity pattern and social behavior

EDC exposure has been demonstrated to impact locomotor activity as well as social or reproductive behaviors in a range of species (Colman et al., 2009; Patisaul and Adewale, 2009; Saili et al., 2012). Critical components of behavioral regulation by the circadian system include sleep / wake patterns, locomotor activity patterns and timing of food intake. The molecular clock drives behavioral rhythmicity and influences overall activity level. In mice lacking *bmal1*, locomotor activity pattern was abolished under constant darkness and overall activity level was reduced (Bunger et al., 2000). Locomotor activity pattern and rhythmic feeding behavior have been described to persist under constant conditions in fish, indicating that these processes can be endogenously circadian, rather than occurring only in response to light – dark cycle or feeding time (Iigo and Tabata, 1996; Mata-Sotres et al., 2015). Sex steroids play an integral role in modulating behavioral patterns. Circadian activity patterns are strongly sexually dimorphic, with phase, amplitude and period modulated by both estrogens and androgens (Krizo and Mintz, 2015). Estrogen signaling during development programs sexually dimorphic behaviors in adult mice (Royston et al., 2016), reviewed in (Hatcher et al., 2018). Estrogen signaling modulates behavioral rhythmicity in adulthood as well and estrogen action via ER directly modulates clock gene expression in the SCN and in peripheral tissues (Hatcher et al., 2018; Royston et al., 2014) and Table 3. In male and female rodents, gonadal steroids modulate locomotor activity rhythm, time of activity onset and overall activity levels (Daan et al., 1975; Juárez-Tapia and Miranda-Anaya, 2017; Karatsoreos et al., 2007; Morin et al., 1977).

The studies presented in this section demonstrate perturbed locomotor and behavioral rhythmicity following EDC exposure. Progesterone exposure resulted in dose-dependent dampening of circadian rhythm of locomotor activity in zebrafish eleuthero embryos, as measured under constant darkness conditions (Zhao et al., 2018). In adult zebrafish, bisphenol A (BPA) and estradiol (E2) altered circadian rhythm of light / dark preference, and E2 dampened locomotor activity pattern (Wang et al., 2015). Developmental BPA exposure reduced total activity level and altered circadian activity pattern in adult male zebrafish, with no comparable impact observed in females (Weber et al., 2015). Dietary polychlorinated biphenyls (PCBs) altered swimming activity pattern in adult zebrafish and their offspring (Péan et al., 2013) and in goldfish, lithium chloride perturbed circadian locomotor activity rhythm (Kavaliers, 1981). Corresponding behavioral phenotypes were reported following EDC exposure, for example, reduced aggressive behavior and decreased group preference (Wang et al., 2015), increased anxiety (Porseryd et al., 2017), sexually dimorphic alteration to social behavior (Weber et al., 2015) and altered shoaling behaviors (Kavaliers, 1981; Porseryd et al., 2017). Whether there is a circadian component to these social behaviors is less clear due to limitations of experimental design in the studies described and certainly warrants future exploration. Some evidence exists for circadian control of social behaviors; an endogenous social rhythm was found to persist under constant conditions in C57BL/6J mice and entrain to the light-dark cycle (Panksepp et al., 2008).

In rodent models, exposure to a hydroxylated PCB metabolite in male Wistar rats increased locomotor activity during both light and dark phases, but it is unclear whether this was a circadian impact or general hyperactivity (Lesmana et al., 2014). The pharmaceutical triazolam induced a phase advance in circadian locomotor activity rhythm in golden hamsters, which corresponded with dysregulating timing of LH surge (Turek, 1988). In male C57BL/6J mice, dietary exposure to the fungicide tolyfluanid impacted diurnal circadian activity pattern (Regnier et al., 2015). Altered diurnal rhythm of energy expenditure and food intake was reported, with exposed mice exhibiting increased food consumption, activity and energy expenditure during the light phase. The study revealed a link between activity rhythm and feeding pattern and perturbed energy homeostasis. Exposed mice exhibited increased body weight and adiposity, glucose intolerance, insulin resistance and impaired metabolic flexibility. Evidence of parallel circadian and metabolic disruption following EDC exposure will be further explored in the following section.

5. EDC exposure and metabolic disruption

Extensive metabolic dysregulation has been documented as a result of EDC exposure in humans and model organisms, with epidemiological and mechanistic links to obesity, diabetes and metabolic syndrome (Heindel et al., 2017; Veiga-Lopez et al., 2018). Nuclear receptors are targets of EDC binding, and perturbed NR signaling plays a central role in mediating diabetogenic and obesogenic action of EDCs (Casals-Casas and Desvergne, 2011). EDC exposure and circadian disruption induce similar metabolic pathologies (Bass and Lazar, 2016; Heindel et al., 2017), but the extent to which circadian clocks mediate EDC action is not well characterized. In the following sections, we will explore crosstalk among circadian and endocrine systems in controlling metabolism and evidence of parallel metabolic and circadian disruption following EDC exposure across organisms.

5.1 Circadian clocks regulate metabolic and energetic homeostasis

The circadian system is a critical regulator of metabolic and energetic homeostasis. Temporal separation of incompatible metabolic processes such as catabolism vs. anabolism and redox processes helps prevent futile cycling and contributes to energetic homeostasis (Bass and Takahashi, 2010). Central and peripheral clocks modulate lipid metabolism, glucose homeostasis, body weight and energy metabolism (Froy and Garaulet, 2018; Gooley, 2016; Lamia et al., 2008; O'Neill and Feeney, 2013). In humans, circadian disruption such as seen in shift work impacts energy homeostasis, leading to metabolic pathologies such as obesity, diabetes and metabolic syndrome (Table 1). In rodent models, core clock gene ablation causes extensive perturbation of metabolic health and energy homeostasis, leading to a range of diabetogenic and obesogenic phenotypes following systemic as well as liver, pancreas or adipose-specific gene ablation (Table 2). Environmental circadian disruption in rodent models via light at night or simulated shift work impairs pancreatic clock function, leading to islet failure and type 2 diabetes mellitus (Gale et al., 2011; Qian et al., 2013). Pancreatic islets from type 2 diabetic patients grown *in vitro* were found to have dampened circadian oscillation and deficits in insulin and glucagon exocytosis compared with controls (Petrenko et al., 2020). Obesogenic diet as well as altered feeding rhythms have been extensively characterized to perturb clock gene expression and

dysregulate metabolism in metabolically active tissues (Cunningham et al., 2016; Engin, 2017; Fonken et al., 2013; Guan et al., 2018; Qian et al., 2015; Salgado-Delgado et al., 2013).

5.2 Nuclear receptor signaling integrates circadian and endocrine control of metabolism

Nuclear receptors exhibit rhythmic expression patterns in metabolic tissues, and can directly modulate clock gene expression (Teboul et al., 2008; Yang et al., 2006) (Table 3 **and** Figure 2). Nuclear receptors Reverb-α/β, and RORα/β/γ form secondary regulatory feedback loops to the molecular clock and function in regulation of circadian rhythm and metabolism (Guillaumond et al., 2005). Reverb-α regulates glucagon secretion in pancreatic alpha cells and mediates rhythmic cholesterol, lipid and bile acid metabolism in liver (Martelot et al., 2009; Vieira et al., 2013). Adrenal glucocorticoids regulate clock gene expression in brain and a range of peripheral tissues, and modulate rhythmic metabolic processes in liver (Table 3) (Quagliarini et al., 2019; So et al., 2009). Nutrient and metabolite sensing nuclear receptors such as PPARs, constitutive androstane receptor (CAR), liver X receptor (LXR) and farnesoid X receptor (FXR) mediate nutrient, lipid and energy metabolic pathways (Preidis et al., n.d.; Xu et al., 2018). PPARα/γ directly modulate core clock gene expression and are critical molecular links between peripheral clocks and energetic homeostasis (Table 3 **and** Figure 2) (Chen and Yang, 2014; Yang et al., 2012). Some metabolite sensing receptors such as LXR are expressed in multiple endocrine organs and can modulate both metabolic and endocrine processes such as glucose homeostasis and insulin sensitivity, and gonadal steroidogenesis, among others (Maqdasy et al., 2016). For a detailed review of endocrine / neuroendocrine control of metabolism in the context of EDC action, see (Heindel et al., 2017).

5.3 Parallel circadian and metabolic dysregulation following EDC exposure

Two studies explored transcriptional and physiological responses following exposure to EDCs or an obesogenic diet. Kopp et al. (2017) assessed lipid accumulation and circadian rhythm in zebrafish following developmental exposure to a range of obesogenic EDCs or to high calorie diet (HCD). The study was conducted in a transgenic zebrafish line containing a luciferase reporter driven by 4 E-boxes, representing binding sites for the core clock transcriptional activator and heterodimer Clock / Bmal1. Two compounds, benzophenone-3 and tetrabrominated bisphenol A, abolished rhythmicity of luciferase expression in the transgenic zebrafish model, as did HCD control. Exposure to tributylin and tris (1,3-dichloroisopropyl) phosphate resulted in altered amplitude and periodicity of the luciferase reporter. Dietary EDC exposure resulted in a greater extent of lipid accumulation than HCD in zebrafish larvae (Kopp et al., 2017). Labaronne et al. (2017) examined transcriptional responses in mouse liver following lifelong exposure to low dose pollutant mixture vs. a high fat, high sucrose (HFHS) diet. Circadian rhythm signaling was significantly perturbed by low dose pollutant exposure, with downregulation of positive elements of the clock (c*lock, nr1d1* and *bmal1*) and upregulation of negative elements of the clock (*per1, per2, per3, cry2, nr1d2* and *rorc*). A similar pattern of clock gene perturbation was observed in the HFHS diet fed mice, but with fewer genes significantly impacted. Other pathways dysregulated by low dose pollutant exposure or HFHS diet include drug and xenobiotic

metabolism, steroid biosynthesis, and fatty acid metabolism, with overlapping but not identical gene sets contributing to these pathway impacts (Labaronne et al., 2017).

Fader et al. (2019) conducted a circadian time-course sample collection to examine impact of oral 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) exposure on hepatic transcript and metabolite rhythmicity in male C57BL/6J mice. Transcript and protein-level cycling of several core clock genes including *bmal1, clock, nr1d1, per1, cry1*, and *nfil3* was impacted by TCDD exposure in a dose-dependent manner, exhibiting reduced amplitude or loss of cycling. TCDD exposure also resulted in an almost complete collapse of clock-controlled hepatic transcript and metabolite cycling. Pathways impacted by TCDD exposure in liver included lipid metabolism, glucose / glycogen metabolism and heme metabolism. The results indicated diminished metabolic efficiency and energy storage following TCDD exposure in liver (Fader et al., 2019). As discussed in the previous section, exposure to the fungicide tolyfluanid in C57BL/6J mice altered diurnal rhythm of energy expenditure and food intake and led to increased body weight, impaired metabolic flexibility, glucose intolerance and insulin resistance (Regnier et al., 2015). Circadian rhythm signaling was the most significantly dysregulated pathway following exposure to a hydroxylated PCB congener in liver of adult male Wistar rats (Ochiai et al., 2018), and core clock gene expression was perturbed in liver of B6C3F1 male mice following oral exposure to Di-2-ethylhexyl phthalate (DEHP), with a corresponding increase in liver weight following 48 and 72 hour exposures. (Currie et al., 2005). *In vitro*, bisphenol A exposure altered core clock gene expression and dysregulated neuropeptide expression in feeding-related neurons of the hypothalamus; altered neuropeptide Y expression following BPA exposure was dependent on the presence of *bmal1* (Loganathan et al., 2019)

6. Xenobiotic sensing through aryl hydrocarbon receptor

Per-Arnt-Sim (PAS)-domain containing proteins function as environmental sensors. Members of this protein family include elements of the molecular clock as well as aryl hydrocarbon receptor (AhR) and hypoxia-sensing proteins, such as the hypoxia-inducible factors (HIFs) (Hahn et al., 2017; McIntosh et al., 2010; Pelster and Egg, 2018). Crosstalk between hypoxia response and circadian rhythm transcription factors has been documented at the molecular level (Pelster and Egg, 2018), and crosstalk between AhR and clock proteins has been described in mammalian models (Mukai and Tischkau, 2007; Xu et al., 2010). AhR functions as a xenobiotic sensor, directing cellular response to xenobiotic exposure. Known agonists of AhR include dioxin, polycyclic aromatic hydrocarbons, dioxin-like polychlorinated biphenyl congeners, some pharmaceuticals and endogenous and dietary ligands such as plant flavonoids and photo-oxidation products of tryptophan (Denison and Nagy, 2003). Circadian control of xenobiotic sensor and drug metabolizing gene expression patterns imparts a temporal component to detoxification processes. Expression patterns of the drug processing gene battery as well as xenobiotic and nutrient sensing nuclear receptors CAR, PXR, AhR and its binding partner ARNT and PPARα are rhythmic in mouse liver, with circadian expression patterns found to vary based on sex (Huang et al., 2002; Lu et al., 2013; Y.-K. J. Zhang et al., 2009). Rhythmic expression patterns of drug metabolizing genes and AhR are also observed in zebrafish liver (Carmona-Antoñanzas et al., 2017). Crosstalk between core clock proteins and AhR modulates the

AhR-induced detoxification response. In mouse lungs, *Clock* modulated transcriptional response to AhR ligand benzo[a]pyrene and induction of detoxification enzymes, and *per1* and *per2* modulated transcriptional response to dioxin in mouse mammary gland and liver (Qu et al., 2010; Tanimura et al., 2011). AhR additionally intersects with hormone and nutrient-sensing receptors such as ER and PPARs in mediating xenobiotic response (Casals-Casas and Desvergne, 2011; La Merrill Michele et al., 2013; Swedenborg and Pongratz, 2010). The studies described in this section explored physiological and circadian impacts of AhR activation.

Altered circadian transcriptional or behavioral rhythms have been observed in rodent models following AhR activation by TCDD. TCDD altered core clock gene expression or transcriptional rhythm in mouse liver, SCN and ovary of C57BL/6J mice (Mukai et al., 2008; Tischkau et al., 2011; Xu et al., 2010). TCDD-exposed mice exhibited decreased phase shifts in response to light (Mukai et al., 2008). In deer mice, TCDD disrupted rest-activity rhythm and altered transcriptional rhythm of core clock genes in the SCN (Miller et al., 1999). In female C57BL/6J mice, TCDD exposure disrupted 24-hour rhythm of progenitor hematopoietic stem cell numbers, and perturbed transcriptional rhythm of *per1* and *per2* in progenitor stem cell populations (Garrett and Gasiewicz, 2006). As discussed in the previous section, TCDD exposure perturbed core clock gene cycling in liver as well as hepatic transcriptome and metabolome rhythmicity in male C57BL/6J mice (Fader et al., 2019). The PAH β-naphthoflavone (BNF) reduced light-induced phase shifts in C57BL/6J mice, and response was dependent on the presence of AhR (Xu et al., 2013). In Rainbow trout, PAH exposure altered diurnal variation of melatonin, serotonin and other neurotransmitters in the pineal gland (Gesto et al., 2009). While PAHs are characterized as AhR agonists, it is not clear whether findings reported in this study involved AhR activation.

Interactions of xenobiotic and hypoxia responses were explored following exposure to the pharmaceutical diclofenac in wild-caught three-spined stickleback (Prokkola et al., 2015). Exposure to both hypoxia and diclofenac, but not combination, resulted in altered expression level and dampened oscillation of *per1* and *clock.* Both individual and combined exposures led to AhR activation, and diclofenac exposure in combination with hypoxia interfered with the expected hypoxia response (Prokkola et al., 2015). The nature of the interaction between activated AhR and other PAS-domain containing proteins across organisms and in various xenobiotic exposure contexts warrants future exploration. Additional circadian impacts of xenobiotic exposure have been demonstrated following exposure to pharmaceuticals and anxiolytic drugs (Akiyama et al., 1999; Kavaliers, 1981; Oggier et al., 2010; Xiao et al., 2017) and to copper (Doria et al., 2018; Kim et al., 2017; Vicario-Parés et al., 2018). While pharmaceuticals, PAHs and some heavy metals are not primarily classified as EDCs, some pollutants within these classes have known endocrine activity (Handy, 2003; Overturf et al., 2016; Sabir et al., 2019; Toppari and Juul, 2010; Y. Zhang et al., 2016); studies summarized in Table 4 indicate pollutants from these classes that may additionally interact with circadian systems.

7. Perspectives and Outlook

There is a small but growing body of evidence of the potential for EDCs to disrupt endocrine and circadian systems in parallel. The studies discussed in this review demonstrate circadian impacts of EDCs in three major contexts: rhythmic physiology in the HPG(L) axis, locomotor and behavioral rhythms, and metabolic and energetic homeostasis. Figure 3 summarizes physiological perturbations following EDC exposure in the reviewed studies. EDC exposure alters expression level of core clock and circadian rhythm network genes, perturbs transcriptional and metabolite rhythmicity in brain and / or peripheral organs and alters locomotor and behavioral rhythms (Table 4). The extent to which circadian systems modulate reproductive, metabolic/energetic and behavioral impacts of EDCs warrants further exploration. While extensive bidirectional molecular crosstalk between circadian and endocrine systems has been described, mechanistic links between EDC exposure and perturbations to the core clock and clock-driven physiology remain to be elucidated. In this review, we aimed to highlight parallel circadian and endocrine impacts following EDC exposure across species and propose a call for future research to explore mechanisms driving these observations.

Across species, EDCs strongly perturbed core clock and circadian rhythm network gene transcription in the reproductive axis, and rhythmic physiology, such as gonadotropin release from pituitary, was impacted as well. EDC exposure characteristically reduced fecundity, and circadian transcriptional impacts were observed to a greater extent following exposure to EDC mixtures. Endocrine rhythms in the reproductive axis range from short (hourly) to long-term (seasonal). Across species, there is a balance of growth and energetics vs. reproduction (Fernandez-Fernandez et al., 2006; Wade et al., 1996; D. Zhang et al., 2009). Timing of reproduction is critical, particularly in species exhibiting seasonal reproductive cycles, and variation in susceptibility to EDC action based on timing of exposure remains to be further clarified.

Natural rhythms of behavior and group social behaviors are crucial for safety, predator avoidance, survival and reproductive success across species. The circadian clock drives behavioral rhythms to adapt physiology to the 24-hour light / dark cycle. A limited number of studies demonstrated EDC-induced impacts on circadian rhythm of locomotor activity, energy expenditure or food intake across organisms. EDCs altered social behaviors in teleost fish, including group preference, cohesive shoal formation, aggression and ability to adapt to a new environment. Whether there is a circadian component to these social behaviors is less clear due to limitations of experimental design in the studies described and certainly merits future exploration. Circadian regulation of social and reproductive behaviors has been described, and EDC exposure can alter sexual behaviors in fish (Feng and Bass, 2016; Panksepp et al., 2008; Rubow and Bass, 2009; Söffker and Tyler, 2012). Further, circadian patterns of locomotor activity and feeding are interconnected with metabolic health (Engin, 2017; Regnier et al., 2015).

The circadian clock is intimately connected with energetic and metabolic homeostasis. Steroidogenic, xenobiotic, redox and lipid metabolic pathways, among others, are subject to circadian control (Carmona-Antoñanzas et al., 2017; Gooley, 2016; Johnson et al., 2014;

O'Neill and Feeney, 2013; Son et al., 2008). The tight coupling between circadian and metabolic oscillations is mediated through a variety of mechanisms, including NAD-dependent enzymes as well as nutrient, redox and temperature-sensing factors (Asher and Schibler, 2011). Signaling through nuclear receptors modulates energetic homeostasis and exerts feedback on the clock in metabolically active tissues (Preidis et al., n.d.; Yang et al., 2012, 2006). Comparing organismal responses to EDCs and obesogenic diet provides insight into overlapping transcriptional responses and phenotypes of metabolic and circadian disruption (Kopp et al., 2017; Labaronne et al., 2017). Altered lipid metabolism in particular is implicated in obesogenic action of EDCs across species (Carnevali et al., 2017; Maradonna and Carnevali, 2018). Given the critical role of nuclear receptors in orchestrating metabolic processes and the ability of EDCs to signal through NRs, experimental design aimed at characterizing rhythmic physiology of EDC / NR interactions will be helpful in delineating obesogenic mode of action of EDCs. Additional physiological impacts of EDCs include perturbation of circadian temperature rhythm (Johnstone et al., 2013), redox metabolism (Jiménez-Ortega et al., 2012), and immune response (Faltermann et al., 2014; Xiao et al., 2017; Zhao et al., 2016). Circadian impacts of EDC exposure were sexually dimorphic as well as transgenerational (Walker et al., 2014; Zhao et al., 2015a).

Future research is needed to investigate EDC action in the context of endogenous biological rhythms and whether parallel circadian disruption plays a role in exacerbating or driving endocrine pathologies. Extensive bidirectional crosstalk exists between circadian clocks and endocrine signaling. Gonadotropins, adrenal and gonadal steroids, PPAR ligands and retinoids via nuclear receptor signaling directly regulate core clock gene expression and modulate circadian rhythmicity in brain and peripheral organs (Table 3 and Figure 2). Whether EDCs activate similar signaling pathways and directly modulate clock function warrants future exploration. Characterizing NR and AhR crosstalk with the molecular clock in the context of EDC exposure may prove crucial to understanding the nature of interaction between circadian and endocrine systems in mediating EDC effects. Characterizing circadian physiology in the context of life-stage dependent, multigenerational and seasonal effects of EDCs will also aid in understanding windows of vulnerability to EDC action across species.

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Circadian clock gene abbreviations:

clock:	circadian locomoter output cycles protein kaput

arntl / bmal1:	'aryl hydrocarbon receptor nuclear translocator-like protein 1' also known as 'brain and muscle ARNT-like 1'
per1:	period circadian protein homolog 1
per2:	period circadian protein homolog 2
per3:	period circadian protein homolog 3
cry1:	cryptochrome circadian regulator 1
cry2:	cryptochrome circadian regulator 2
nr1d1:	nuclear receptor subfamily 1 group d member 1, also known as Rev-erbα
nr1d2:	nuclear receptor subfamily 1 group d member 2, also known as Rev-erbβ
rorc:	RAR-related orphan receptor c
nfil3:	nuclear factor interleukin-3-regulated protein
npas2:	neuronal PAS-domain containing protein 2

Nuclear and xenobiotic sensing receptor abbreviations:

ERα:	estrogen receptor alpha
PR:	progesterone receptor
AR:	androgen receptor
ERRα:	estrogen-related receptor alpha
GR:	glucocorticoid receptor
FXR:	farnesoid X receptor
LXR:	liver X receptor
PXR:	pregnane X receptor
CAR:	constitutive androstane receptor
PPARα/γ:	peroxisome proliferator-activated receptor alpha / gamma
RARα:	retinoic acid receptor alpha
RXR:	retinoid X receptor
RORα/β/γ:	retinoic acid-related orphan receptor alpha / beta / gamma
AhR:	aryl hydrocarbon receptor

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Highlights

- Circadian clocks generate biological rhythms important for homeostatic control
- Endocrine disrupting chemicals perturb endocrine and circadian systems in parallel
- Nuclear receptors are targeted by EDCs and exert feedback on circadian clocks
- EDCs perturb circadian reproductive physiology, behavior and metabolism

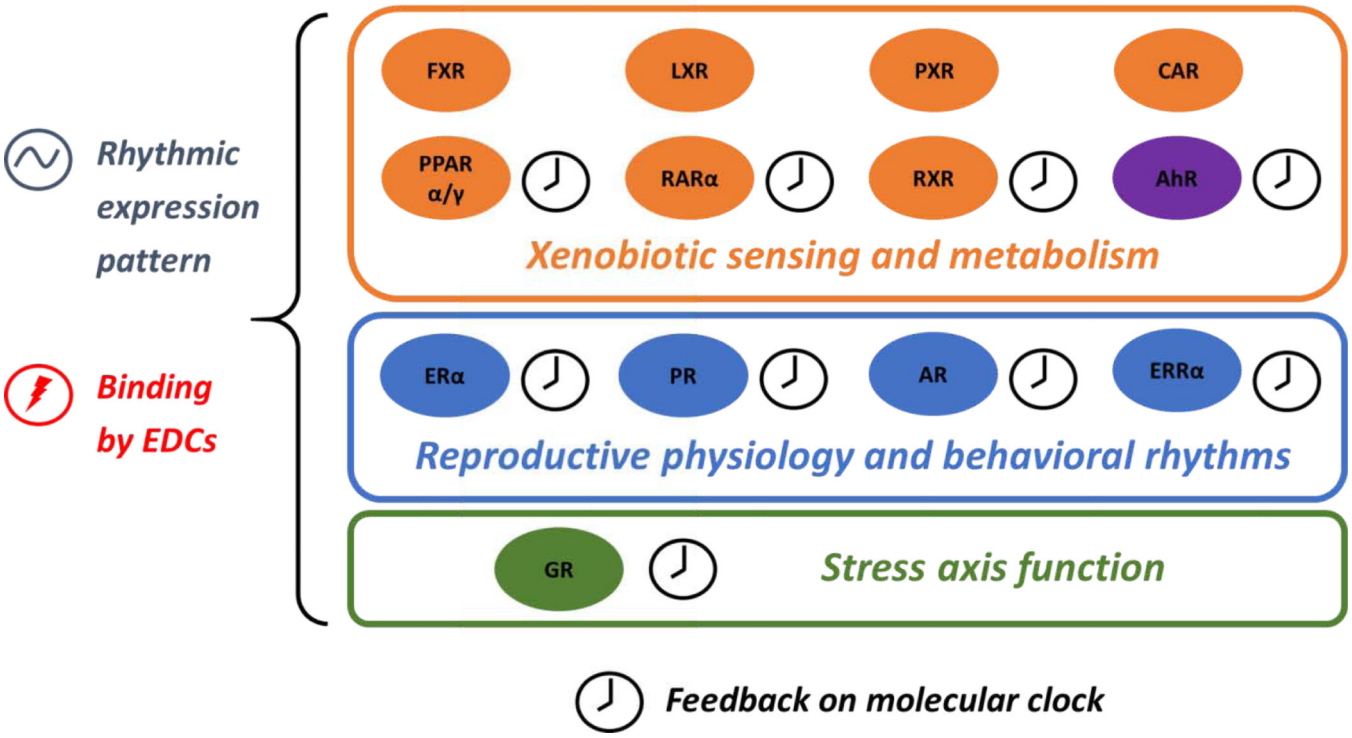

Figure 1. Nuclear receptors exhibit rhythmic expression patterns, are targets of EDCs and exert feedback on the molecular clock.

Nuclear receptors and aryl hydrocarbon receptor (AhR) mediate physiological functions ranging from xenobiotic sensing and metabolism to reproductive physiology, behavioral rhythms and stress axis function. Nuclear receptors and AhR are clock-controlled and have been extensively documented as targets of EDC binding. A clock icon indicates nuclear receptors found to exert direct feedback on the mammalian molecular clock. Studies demonstrating NR-clock crosstalk are detailed in Table 3.

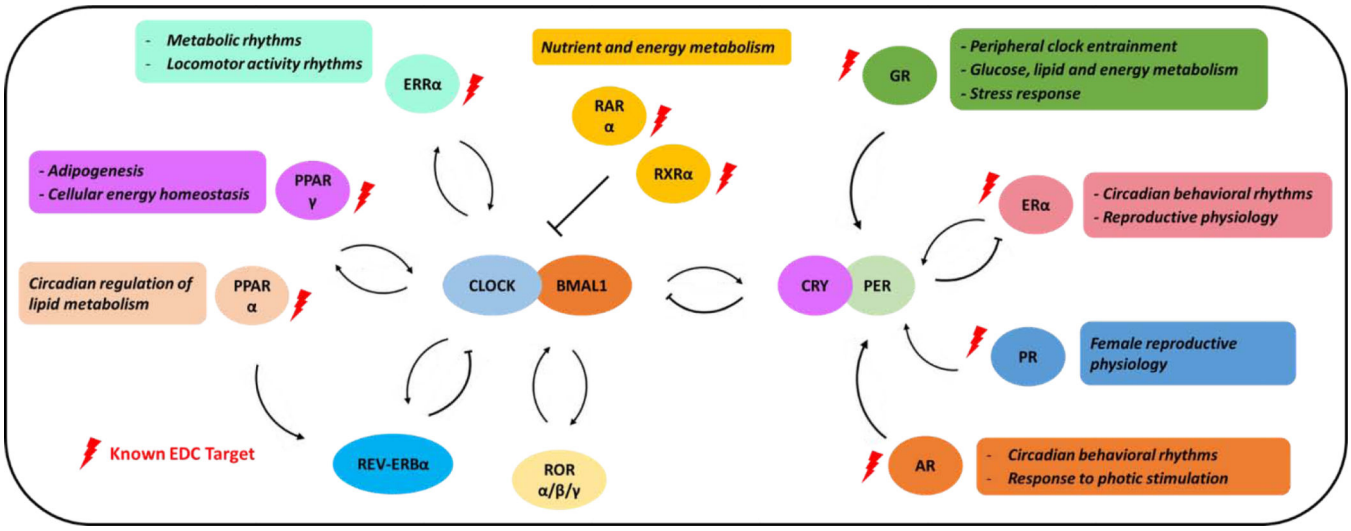

Figure 2. Bidirectional relationship between nuclear receptor signaling pathways and the mammalian circadian clock.

The molecular clock consists of an activator arm (CLOCK:BMAL1 heterodimer) driving transcription of clock-controlled genes as well as negative clock elements PER and CRY, which repress CLOCK:BMAL1 transcriptional activity with a periodicity of approximately 24 hours. Rev-Erb and ROR proteins are nuclear receptors that constitute secondary feedback loops to the core molecular clock. Several steroid hormone, nutrient and metabolite sensing nuclear receptors directly modulate clock gene expression and circadian physiological processes in mammals, and are known targets of EDC binding. Figure adapted from (Teboul et al., 2009).

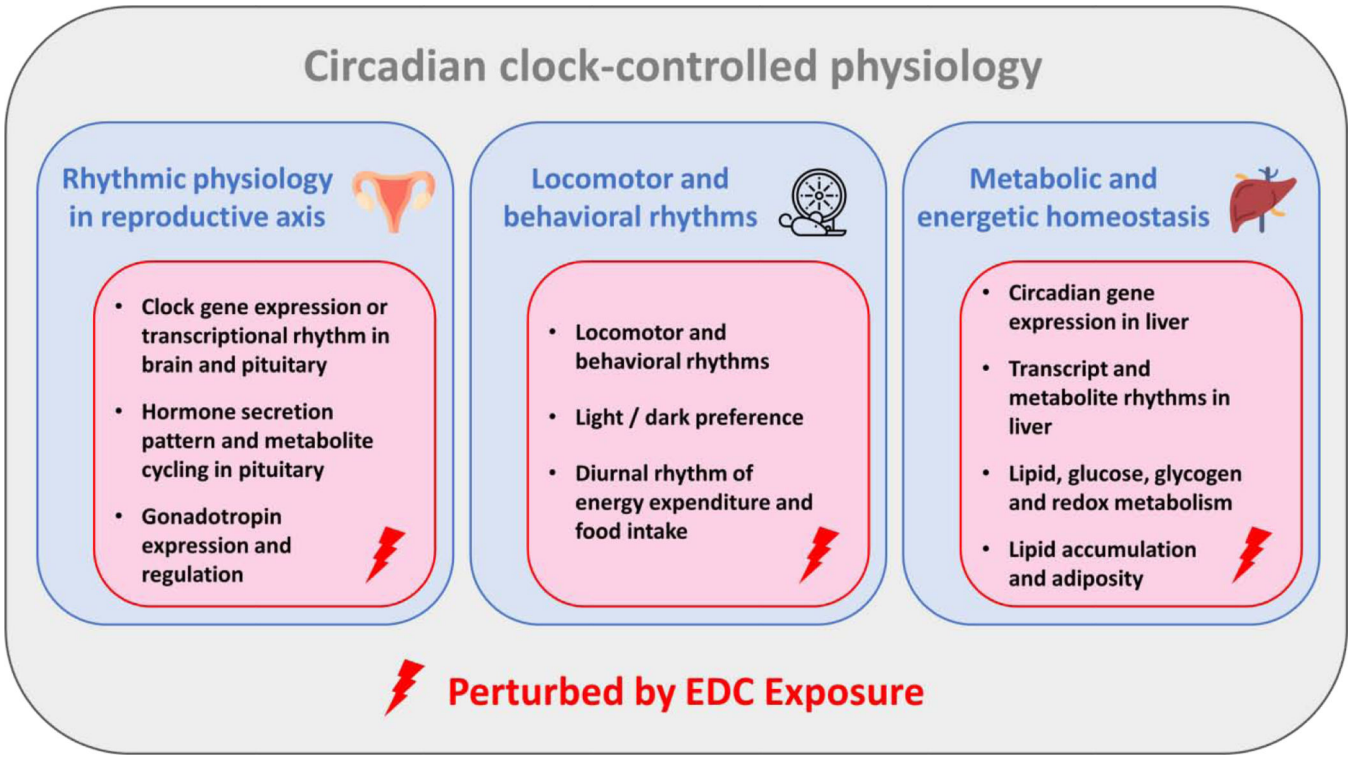

Figure 3. Summary of physiological perturbations following EDC exposure in the reviewed studies.

Across species, circadian clocks modulate reproductive, behavioral, and metabolic rhythms. The reviewed studies demonstrate a range of perturbations to circadian transcriptional or physiological rhythms following EDC exposure. In the reproductive axis, EDCs alter transcriptional rhythms, hormone secretion patterns and metabolite cycling. EDCs alter locomotor and behavioral rhythms as well as diurnal rhythms of energy expenditure and food intake. EDC exposure results in altered transcript and metabolite cycling in liver, lipid and glucose dysregulations and impaired energetic homeostasis.

Table 1.

Association of shift work and circadian gene variance with altered endocrine physiology in human populations

Category	Exposure	Physiological perturbation	References
Metabolic dysregulation	Shift work	Increased risk of diabetes mellitus	(Gan et al., 2015; Morikawa et al., 2005; Pan et al., 2011; Suwazono et al., 2006)
		Impaired energy handling	(Oyama et al., 2012; Suwazono et al., 2009)
		Increased risk of metabolic syndrome, association with BMI and lipid disturbances	(De Bacquer et al., 2009; Esquirol et al., 2009; Ha and Park, 2005; Karlsson et al., 2001, 2003; Lin et al., 2009; Morikawa et al., 2007; Pietroiusti et al., 2010; Sookoian et al., 2007) In submariner population: (Kang and Song, 2018)
	Circadian gene variance	*bmal1* and *npas2* gene variants linked to seasonal variation of sleep, social activity, mood, weight, appetite and energy level	(Kovanen et al., 2010)
Endocrine cancer	Shift work	Increased breast cancer risk	(He et al., 2015; Jia et al., 2013; Wang et al., 2013; Wegrzyn et al., 2017)
	Circadian gene variance	Circadian gene polymorphism or expression level associated with breast cancer prognosis and survival	(Cadenas et al., 2014; Escala-Garcia et al., 2020; Yi et al., 2010)
		Clock gene polymorphism associated with breast cancer risk	(Hoffman et al., 2010; Truong et al., 2014)
		Cadmium exposure and *clock* variant genotype associated with risk of thyroid cancer and tumor severity	(Q. Zhang et al., 2019)
	Epigenetic control of circadian genes	Altered methylation of circadian genes observed in shift workers	(Samulin Erdem et al., 2017; Zhu et al., 2011)
		Clock gene methylation status associated with breast cancer prognosis	(Kuo et al., 2009)
Reproductive physiology and fertility	Shift work	Irregular ovarian cycle pattern	(Chung et al., 2005; Labyak et al., 2002; Lawson et al., 2011; Lohstroh Pete N et al., 2003; Wan and Chung, 2012)
		Increased risk of endometriosis	(Marino et al., 2008)
		Prolonged wait time to pregnancy	(Bisanti et al., 1996)
	Circadian gene variance	*bmal1* and *npas2* gene variants linked to fertility (number of pregnancies and miscarriage rate)	(Kovanen et al., 2010)
		Altered expression level of *bmal1* in granulosa cells of women diagnosed with polycystic ovary syndrome compared with controls	(J. Zhang et al., 2016)

Table 2.

Endocrine phenotypes of core clock gene knockout in rodent models

Category	Clock gene	Tissue specificity of gene ablation	Gender	Phenotype	Reference
Metabolic dysregulation	*bmal1*	Pancreas-specific	Males	Diabetes due to loss of glucose-stimulated insulin secretion in pancreatic islets; ROS accumulation and mitochondrial uncoupling in islets	(Lee et al., 2013)
		Systemic	Males	Insulin-resistant, loss of rhythmicity in insulin action, prone to obesity on high-fat diet	(Shi et al., 2013)
		Adipocyte - specific	Males	Shift in diurnal rhythm of food intake and obesity	(Paschos et al., 2012)
		Pancreas-specific	Not specified	Glucose intolerance and defective insulin production, defective glucose-stimulated insulin secretion in isolated pancreatic islets	(Sadacca et al., 2011)
		Pancreas-specific	Males and females	Poor metabolic adaptation to high fat diet, fasting and diurnal hyperglycemia, glucose intolerance, loss of glucose-stimulated insulin secretion, impaired beta cell expansion and regeneration potential	(Rakshit et al., 2016)
		Liver-specific	Males	Hypoglycemia in fasting phase, altered glucose clearance and loss of rhythmicity in hepatic glucose regulatory genes	(Lamia et al., 2008)
	clock and bmal1	Systemic and pancreas-specific	Males	Impaired glucose tolerance, reduced insulin secretion and deficits in pancreatic function	(Marcheva et al., 2010)
		Systemic	Not specified	Altered insulin tolerance, impaired gluconeogenesis, altered glucose homeostasis	(Rudic et al., 2004)
	clock	Systemic	Males	Altered diurnal feeding rhythm, obesity, hyperlipidemia, hepatic steatosis and hyperglycemia	(Turek et al., 2005)
	per2	Systemic	Males	Elevated plasma insulin levels, enhanced glucose-stimulated insulin secretion and impaired insulin clearance	(Zhao et al., 2012)
	cry1 and cry2	Systemic	Males	High-fat diet induced hyperinsulinemia and tissue-specific insulin resistance	(Barclay et al., 2013)
HPA axis, adrenal steroidogenes is	*bmal1*	Adrenal-specific	Males and females	Sexually dimorphic perturbation in stress response following adrenal Bmal1 deletion; altered response to ACTH	(Engeland et al., 2019)
		Adrenal-specific	Males	Disruption of rhythmic steroidogenic gene expression; behavior and physiological rhythms and acute stress response not impacted	(Dumbell et al., 2016)
		Systemic	Males	Reduced serum cortisol levels; impaired adrenal responsiveness to ACTH; impaired adrenal steroidogenesis; diminished GC and behavioral response to stress	(Leliavski et al., 2014)
		Adrenal-specific	Males	Disrupted circadian GC production; altered behavioral rhythmicity, altered expression of Per2 in several peripheral organs	(Son et al., 2008)
	per2 and cry1	Systemic	Males	Deficient HPA axis regulation; impaired response to ACTH simulation of corticosteroid production	(Oster et al., 2006)
Reproductive physiology and fertility	*bmal1*	Systemic	Females	Impaired oocyte fertilization rate, early embryo development and implantation potential in female mice	(Xu et al., 2016)

Category	Clock gene	Tissue specificity of gene ablation	Gender	Phenotype	Reference
		Ovary-specific	Females	Altered ovarian LC sensitivity, timing of ovulation and fertility in female mice following conditional Bmal1 deletion in ovarian theca cells	(Mereness et al., 2016)
		Brain, pituitary, adrenal, ovary	Females	Embryonic implantation failure rescued by progesterone supplementation or ovarian transplant; impaired ovarian steroidogenesis	(Liu et al., 2014)
		Systemic and gonadotro pe-specific	Females	Differing effects of global and gonadotrope-specific Bmal1 knockout. Disrupted LH and FSH proestrous surge and altered estrous cycle in global knockout mice; gonadotrope-specific knockout mice had increased variability in estrous cycle length, otherwise reproductively normal	(Chu et al., 2013, p. 1)
		Systemic	Females	Disrupted estrous cycle; reduced serum progesterone levels; impaired ovarian steroidogenesis; implantation failure; exogenous administration of progesterone restores implantation	(Ratajczak et al., 2009)
		Systemic	Males and females	Male and female infertility; low testosterone and high LH serum concentrations in males; reduced expression level of steroidogenic genes in male testes	(Alvarez et al., 2008)
	clock	Systemic	Females	Clock mutation in dams disrupted nursing and maternal behavior and impacted growth and survival rate of pups	(Hoshino et al., 2006)
		Systemic	Males and females	Reduced fertility in males; disrupted estrous cycle in females; pregnancy rates and neonatal litter size not affected	(Dolatshad et al., 2006)
		Systemic	Females	Disrupted estrous cycle; impaired LH surge; increased rate of full-term pregnancy failure	(Miller et al., 2004)
	per1 and per2	Systemic	Females	Middle-aged Per mutant females display disrupted estrous cycle and lower reproductive success; potential advance in reproductive aging as a result of loss of Per genes	(Pilorz and Steinlechn er, 2008)

Table 3.

Direct feedback on molecular clock by nuclear receptors in rodent models

Nuclear receptor	Cross-talk with molecular clock	Reference
GR	Physical interaction of CLOCK and GR; direct acetylation of GR by CLOCK suppressed GR transcriptional activity	(Nader et al., 2009)
	Transcriptional regulation of Per2 expression by GR via binding GRE in Per2 promotor; GREs also identified in Per1 and E4bp4 gene promotors	(So et al., 2009)
	Transcriptional regulation of Rev-erbα expression by GR	(Torra et al., 2000)
	Rhythmic repression of GR by Cry1 and Cry2	(Lamia et al., 2011)
	Functional GRE in Per1 regulatory region (stress modulated function)	(Yamamoto et al., 2005)
PPARα	Interaction of Per2 with PPARα and Rev-erbα; Per2 coregulates NR-mediated transcription	(Schmutz et al., 2010)
	Direct binding of PPARα on a potential PPARE located in the BMAL1 promotor	(Canaple et al., 2006)
	CLOCK/BMAL1 regulates lipid metabolism via transactivation of the PPARE (mouse intestine)	(Inoue et al., 2005)
PPARα/RXRα	CLOCK/BMAL1-mediated transcription of PER and CRY modulated by PPARα/RXRα	(K. Nakamura et al., 2008)
RARα and RXRα	Retinoic acids via RARα upregulate Per1, Per2 and PPARα expression in an E-box dependent manner	(Shirai et al., 2006)
	Negative regulation of Clock/MOP4:Bmal1 transcriptional activity by RARα and RXRα in vasculature	(McNamara et al., 2001)
ER	Estradiol altered circadian rhythm of Per2 expression in SCN, liver and uterus	(Nakamura et al., 2005)
	Estrogen altered Per2 rhythmic expression in uterus	(T. J. Nakamura et al., 2008)
	Estrogen altered expression of Cry2, but not Cry1 in SCN	(Nakamura et al., 2001)
ER and PR	Estrogen and progesterone altered circadian rhythm of Per2 expression in uterus	(Nakamura et al., 2010)
PR	Full length PRE present in promotor region of NPAS2. P4 regulates expression of several core clock genes in uterus and regulation requires PR	(Rubel et al., 2012)
	PR activates Per1 transcription during human endometrial decidualization	(Y. Zhang et al., 2019)
AR	Androgens modulate light-induced Per2 expression in SCN	(Karatsoreos et al., 2011)
ERRα	Genomic interaction with several core clock genes validated by ChIP-qPCR	(Dufour et al., 2011)

Table 4.

Physiological perturbation following EDC exposure in the reviewed studies

Environmental pollutant	Animal model	Main clock-related finding and associated endocrine or metabolic phenotype	Reference
Environmental steroid hormones			
Progesterone	Female Zebrafish	Altered circadian gene transcription in brain and ovary	(Zucchi et al., 2013)
Progesterone, drospirenone or binary mixture	Female Zebrafish	Altered circadian gene network expression in brain following drospirenone or mixture exposure	(Zucchi et al., 2014)
Progesterone or drospirenone	Zebrafish; adult and F1 generation	Altered circadian rhythm network in adult brain and in F1 eleuthero-embryos; decreased fecundity in adult zebrafish following progesterone exposure	(Zhao et al., 2015a)
Medroxyprogest erone acetate, dydrogesterone and binary mixture	Zebrafish	Altered core clock gene expression in brain, not liver or gonad	(Zhao et al., 2015b)
Progesterone or drospirenone	Zebrafish	Altered circadian rhythm network gene transcription in eyes of adult male and female zebrafish; increased photo transduction signals in eyes of males and females	(Zhao and Fent, 2016)
Estradiol, progesterone and binary mixture	Zebrafish eleuthero embryos	Downregulation of *clock2* and *nr1d1*, upregulation of *nr1d2a* and *cry2a* following some mixtures treatment	(Liang et al., 2019)
17α-ethinylestradiol, norgestrel and binary mixture	Zebrafish eleuthero embryos	Altered core clock gene expression with individual and combined exposures	(Liang et al., 2017)
17a-ethinylestradiol (EE2), antiestrogen ZM 189 or binary mixture	Male fathead minnow	Down regulation of steroidogenic pathway genes and two circadian rhythm network genes following EE2 exposure; distinct expression pattern following co-exposure to EE2 and antiestrogen	(Garcia-Reyero et al., 2009)
17α-Ethinylestradiol (EE2)	Zebrafish	Perturbed circadian rhythm network in female brain; increased anxiety and increased shoal cohesion	(Porseryd et al., 2017)
	Zebrafish	Two genes involved in circadian regulation, *bhlhe40* and *prok2,* upregulated in testes of male zebrafish following developmental EE2 exposure	(Porseryd et al., 2018)
	Female coho salmon	Altered circadian clock gene network in pituitary; transcriptional alterations in gonadotropin regulation, calcium signaling and lipid metabolism	(Harding et al., 2013)
Fludrocortisone acetate	Zebrafish adult, F1 generation and eleuthero embryos	Altered circadian rhythm gene expression across generations; altered glucose homeostasis and immune response gene expression across generations	(Zhao et al., 2016)
20 environmental steroid hormones (7 progestins, 6 corticosteroids, 4 estrogens and 3 androgens	Zebrafish eleuthero embryos	Clock genes downregulated by progestins and corticosteroids, mixed effect of estrogens; *per1a* and *nr1d2a* most strongly dysregulated genes across exposures; progesterone dampens circadian rhythm of locomotor activity in dose-dependent manner; progestins and corticosteroids decreased, and estrogens increased locomotor activity; no apparent impact of androgen exposure on clock gene expression or activity rhythm	(Zhao et al., 2018)
Phenolic EDCs			
4-tert-octylphenol (OP) and bisphenol A (BPA)	Mangrove killfish	Altered transcriptional rhythm of core clock genes in liver of juvenile fish; OP and BPA altered *Km-clock* expression in pituitary / brain, muscle and skin of adult hermaphrodite and secondary male fish, with no effect on gonad or liver	(Rhee et al., 2014)
Bisphenol A	Goldfish	Altered expression of c*ry1*, *per2* and melatonin receptor 1 following BPA exposure	(Choi et al., 2018)
Bisphenol A and estradiol (E2)	Zebrafish	BPA and E2 altered circadian rhythm of light/dark preference; E2 dampened locomotor activity pattern	(Wang et al., 2015)

Environmental pollutant	Animal model	Main clock-related finding and associated endocrine or metabolic phenotype	Reference
Bisphenol A	Zebrafish	Dampened male activity and altered male circadian activity patterns following developmental BPA exposure; sex-specific impact of exposure on social interactions.	(Weber et al., 2015)
Bisphenol A	Neuropeptide expressing hypothalamic cell lines and primary culture	Altered core clock gene expression; altered Neuropeptide Y expression following BPA exposure dependent on presence of *bmal1*	(Loganathan et al., 2019)
2,4-Dichlorophenol	Zebrafish larvae	Alteration in rhythmic expression pattern of core clock genes	(Xiao et al., 2017)
Polychlorinated biphenyls (PCBs)			
Industrial PCB mix Aroclor 1221 (A1221) and estradiol benzoate (EB)	Male and female Sprague-Dawley rats	Upregulation of *bmal1* and *per2* in female AVPV following A1221 and EB exposure; delayed timing of eye opening in females; delayed timing of puberty in males; EB disrupting estrous cycle in females; sexually dimorphic impacts on AVPV and ARC gene expression; masculinized gene expression profile in females	(Walker et al., 2014)
Mixture of non-coplanar PCBs	Zebrafish	Altered swimming activity pattern in adult zebrafish and their offspring	(Péan et al., 2013)
OH-PCB-106	Male Wistar rats	Increased locomotor activity during light and dark phases	(Lesmana et al., 2014)
4-OH-CB107	Male Wistar rats	Transcriptional alteration in circadian rhythm signaling, fatty acid metabolism, drug metabolism, PPAR signaling, chemical carcinogenesis and retinol metabolism in liver	(Ochiai et al., 2018)
Phthalates			
DEHP	B6C3F1 male mice	Transcriptional alteration in circadian rhythm signaling, fatty acid metabolism, steroid metabolism, blood clotting, complement activation and ER overload response in liver	(Currie et al., 2005)
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)			
TCDD	Male Golden hamsters	Altered circadian temperature rhythm	(Gordon et al., 1996)
	Male Long Evans rats		(Gordon and Miller, 1998)
	Rat hypothalamic GnV-3 cell line	Altered 24 h expression pattern of *per1* and *gnrh*; transient induction of Neuropeptide Y expression which requires presence of *AhR*	(Solak et al., 2013)
	C57BL/6J male mice	Decreased phase shifts in response to light; altered expression of *per1* and *bmal1* in SCN and liver	(Mukai et al., 2008)
	C57BL/6J female mice	Altered transcriptional rhythm of *per2* and *bmal1* and *AhR* in ovary; interaction between *AhR* and *bmal1* by co-IP in ovary	(Tischkau et al., 2011)
	Deer mice	Disrupted rest-activity rhythm; altered transcriptional rhythm of *clock* and *per1* in the SCN	(Miller et al., 1999)
	C57BL/6J female mice	Disrupted 24-hour rhythm of progenitor hematopoietic stem cell number; perturbed transcriptional rhythm of *per1* and *per2* in progenitor stem cell populations	(Garrett and Gasiewicz, 2006)
	C57BL/6J male mice	Altered clock gene transcriptional rhythm in liver; almost complete collapse of hepatic transcript and metabolite cycling; diminished metabolic efficiency and energy storage	(Fader et al., 2019)
	C57BL/6J strain male and female *mPer2*^{Luc} mice	No impact on *per2* expression in tissues cultured *ex vivo* from Per2:Luciferase mouse model	(Pendergast and Yamazaki, 2012)
	C57BL/6J male mice and Hepa-1c1c7 and c12 cells	Altered transcriptional rhythm of *per1* in liver; *in vitro*, crosstalk between AhR and CLOCK:BMAL1 mediates *per1* gene suppression	(Xu et al., 2010)
Heavy metals			

Environmental pollutant	Animal model	Main clock-related finding and associated endocrine or metabolic phenotype	Reference
Cadmium	Male Wistar rats	Disrupted transcriptional rhythm of core clock genes in anterior pituitary; altered transcriptional rhythm of redox enzyme expression; altered daily pattern of secreted prolactin, luteinizing hormone, thyrotropin and corticosterone. Clock gene rhythmicity and pituitary hormone secretion patterns partially restored with co-administration of melatonin	(Jiménez-Ortega et al., 2012)
	Male Sprague-Dawley rats	Altered daily pattern of pituitary glutamine, glutamate and aspartate content	(Caride et al., 2010a)
		Disrupted 24-hour secretion pattern of adrenocorticotropic hormone, growth hormone and thyrotropin	(Caride et al., 2010b)
Lead	Fathead minnow	Altered circadian variation of brain neurotransmitters	(Spieler et al., 1995)
Fungicides			
Tolyfluanid	C57BL/6J male mice	Altered diurnal activity pattern; altered diurnal rhythm of energy expenditure and food intake; increased body weight and adiposity, glucose intolerance, insulin resistance and impaired metabolic flexibility	(Regnier et al., 2015)
Climbazole	Zebrafish eleuthero embryos	Transcriptional alterations in circadian rhythm network, steroidogenesis, oocyte maturation and sexual differentiation	(H. Zhang et al., 2019)
Cyanobacterial toxins			
Cyanobacterial toxin CP1020	Zebrafish eleuthero embryos	Transcriptional alteration of circadian rhythm gene network, DNA damage and repair and response to light	(Faltermann et al., 2014)
Cyanotoxins	Medaka	Altered circadian rhythm gene expression in liver; decreased fecundity and egg hatchability; glycogen storage loss and altered energy metabolism in liver	(Qiao et al., 2016)
Microcystis aeruginosa cell extract or purified microcystin-LR (MC-LR)	Zebrafish larvae	*nr1d2b* is the most significantly downregulated gene following microcystis treatment; vitellogenin genes induced by microcystis treatment, but not by purified MC-LR	(Rogers et al., 2011)
Industrial effluent and EDC mixtures			
Pulp and paper mill effluents	Fathead minnow	Altered clock gene expression in hypothalamus of female fish; altered egg production and decreased number of spawning events; results varied by effluent source	(Popesku et al., 2010)
Obesogenic EDCs or high calorie diet	Transgenic zebrafish line containing luciferase reporter driven by 4 E-boxes	Benzophenone-3, tetrabrominated bisphenol A and high calorie diet abolished rhythmicity of luciferase expression; tributylin and tris (1,3)-dichloroisopropyl) phosphate altered amplitude and periodicity of luciferase reporter; lipid accumulation following EDC exposure to a greater extent than high calorie diet	(Kopp et al., 2017)
Low dose pollutant mix or high fat high sucrose diet	C57BL/6J female mice	Transcriptional alteration in circadian rhythm signaling, drug and xenobiotic metabolism, steroid biosynthesis and fatty acid metabolism	(Labaronne et al., 2017)
Influence of sampling time and environmental conditions on EDC response			
Prochloraz	Zebrafish	Impact of prochloraz on hypothalamic – pituitary – gonad – liver (HPGL) axis gene expression and plasma E2 level differs based on sampling time	(Dang et al., 2016)
Perfluorooctane sulfonate (PFOS)	Female Zebrafish	Impact of PFOS on fecundity, plasma E2 level and HPGL axis gene expression differs based on sampling time	(Bao et al., 2019)
17β-estradiol and nonylphenol (NP)	Zebrafish	Temperature and photoperiod modulate induction of estrogen receptor alpha, vitellogenin 1 and 2, and hepatic estrogen-responsive genes following E2 and NP exposure	(Jin et al., 2009)
Other environmental pollutants			
Polycyclic aromatic hydrocarbons (PAH)			

Environmental pollutant	Animal model	Main clock-related finding and associated endocrine or metabolic phenotype	Reference
Naphthalene, benzo(*a*)pyrene and β-naphthoflavone	Rainbow trout	PAH exposure altered diurnal levels of melatonin, serotonin, 5-hydroxyindole-3-acetic acid, 5-hydroxytryptophan and methoxyindole metabolites in pineal organ	(Gesto et al., 2009)
β-naphthoflavone (BNF)	C57BL/6J male mice and AhR knockout mice	BNF reduces light-induced phase shifts; response dependent on AhR	(Xu et al., 2013)
Pharmaceuticals and anxiolytic drugs			
Triazolam	Golden hamster	Phase advance in circadian locomotor activity rhythm and altered timing of LH surge	(Turek, 1988)
Propylthiouracil	Male Long Evans rats	Permanently altered core temperature in adult offspring; non-monotonic impacts on daily temperature rhythm and reduction of mean core temperature at highest dose	(Johnstone et al., 2013)
Diclofenac and hypoxia	Three-spined stickleback	Aryl hydrocarbon receptor activation; altered expression level and dampened oscillation of *per1* and *clock*	(Prokkola et al., 2015)
Lithium chloride	Goldfish	Perturbed circadian locomotor activity rhythm and cohesive shoal formation	(Kavaliers, 1981)
	Zebrafish larvae	Alteration in rhythmic expression pattern of core clock genes	(Xiao et al., 2017)
Diazepam	Zebrafish	Altered circadian rhythm gene network in adult zebrafish and eleuthero-embryos; altered swimming behavior in eleuthero-embryos	(Oggier et al., 2010)
Diazepam, triazolam and tandospirone	ddY male mice	Transient reduction in *per1* expression observed in mouse cerebellum following exposure to benzodiazepines diazepam and triazolam and non-benzodiazepine anxiolytic tandospirone; associated impairment in coordinated movement	(Akiyama et al., 1999)
Copper			
Copper	Zebrafish	Altered transcriptional rhythm of *per1*, *per2* and *cry1a* in liver and brain, with non-monotonic dose effects observed; altered activity and daily expression pattern of antioxidant enzymes superoxide dismutase and catalase	(Doria et al., 2018)
Waterborne copper	Red seabream	Decreased plasma protein levels of Per2 and Cry1 monitored across 36 h	(Kim et al., 2017)
Ionic copper / copper oxide nanoparticles	Zebrafish	Altered clock gene expression in liver	(Vicario-Parés et al., 2018)