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Environmental chemicals affect circadian rhythms: An underexplored effect influencing health and fitness in animals and humans

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ABSTRACT

Circadian rhythms control the life of virtually all organisms. They regulate numerous aspects ranging from cellular processes to reproduction and behavior. Besides the light-dark cycle, there are additional environmental factors that regulate the circadian rhythms in animals as well as humans. Here, we outline the circadian rhythm system and considers zebrafish (*Danio rerio*) as a representative vertebrate organism. We characterize multiple physiological processes, which are affected by circadian rhythm disrupting compounds (circadian disrupters). We focus on and summarize 40 natural and anthropogenic environmental circadian disrupters in fish. They can be divided into six major categories: steroid hormones, metals, pesticides and biocides, polychlorinated biphenyls, neuroactive drugs and other compounds such as cyanobacterial toxins and bisphenol A. Steroid hormones as well as metals are most studied. Especially for progestins and glucocorticoids, circadian dysregulation was demonstrated in zebrafish on the molecular and physiological level, which comprise mainly behavioral alterations. Our review summarizes the current state of knowledge on circadian disrupters, highlights their risks to fish and identifies knowledge gaps in animals and humans. While most studies focus on transcriptional and behavioral alterations, additional effects and consequences are underexplored. Forthcoming studies should explore, which additional environmental circadian disrupters exist. They should clarify the underlying molecular mechanisms and aim to better understand the consequences for physiological processes.

t1. Introduction

Diurnal rhythms are important aspects in plants and animals. The circadian rhythm is an intrinsic timekeeping mechanism that provides organisms to temporally organize behavioral, physiological and molecular events with a 24-hour day/night cycle. Its molecular architecture was first discovered in *Drosophila* and was then revealed to be highly conserved across diverse species (Takahashi, 1992). Circadian rhythm aligns numerous cellular, biochemical, physiological and behavioral processes, including cell division (Matsuo et al., 2003), hormone secretion (Chappell, 2005), nutrient metabolism (Rey and Reddy, 2013), sleep/wake cycle (Beersma and Gordijn, 2007), fertility (Boden and Kennaway, 2006), reproduction (Boden and Kennaway, 2006) and behavior (Hurd et al., 1998). These oscillations are driven by abiotic environmental changes (e.g. light, temperature), as well as internal circadian rhythms, which keep rhythmicity constant by regulating and aligning them, even in the absence of environmental cues (Takahashi et al., 1989). Nearly all vertebrate cells possess self-sustained clocks that couple endogenous rhythms with changes in the environment (Cahill and Hasegawa, 1997). Light-dark cycle is the primary factor controlling the circadian rhythm in organisms (Benstaali et al., 2001). Among additional known factors are temperature (López-Olmeda et al., 2006; Prokkola and Nikinmaa, 2018) and oxygen (Egg et al., 2013).

If the circadian rhythm system is disturbed, physiological dysfunction result. Thereby, the role of contaminants in disturbing circadian interactions in humans and animals is underexplored as previous research was mainly focused on discovering basic principles and aspects. Some environmental chemicals, both natural ones and anthropogenic

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chemicals, which are introduced into surface waters via discharge of industrial, hospital and domestic/municipal wastewater, were shown to interfere with circadian rhythm regulation in aquatic organisms. Such compounds are named circadian disrupters (Fang et al., 2017; Zhao et al., 2020). Although the interaction of environmental chemicals with circadian rhythms is general, in this review, we compile existing data with a focus on fish, particularly on zebrafish as a representative vertebrate model organism, to summarize current knowledge on contaminant-circadian rhythm interactions.

Ecotoxicological studies cover a number of physiological endpoints, including endocrine disruption, reproduction, immune response, organ function, development, neurotoxicity and carcinogenicity (Gerhardt, 2007; Nagel, 2002). However, little attention has so far been paid to circadian rhythms, although they play a crucial role in the development and reproductive performance of aquatic organisms (Bayarri et al., 2009; Blanco-Vives and Sanchez-Vazquez, 2009; Yúfera et al., 2017). Recently, compounds that alter circadian rhythm regulation, called circadian disrupters, to which fish are exposed to and originate mainly from wastewater, have been identified, such as diazepam (Oggier et al., 2010). Particularly, environmental hormones, especially progesterone (Zhao and Fent, 2016a; Zucchi et al., 2013) and synthetic progestins medroxyprogesterone acetate and dydrogesterone (Zhao et al., 2015), as well as glucocorticoids including fludrocortisone acetate (Zhao et al., 2016) and clobetasol propionate (Willi et al., 2019) were shown to adversely target circadian rhythm regulation.

The aim of our present review is to characterize the circadian rhythm regulation in aquatic organisms with emphasis on fish, and subsequently, to critically summarize existing data on circadian disrupters. We emphasize effects in zebrafish that serves as a model organism for fish and mammals. We also point out some implications, particularly considering current knowledge gaps. Our systematic analysis suggests that knowledge about the types of circadian disrupters and their effects in humans and animals is still limited.

A total of 40 environmental substances described in 37 references were identified to interfere with circadian rhythms in fish. They can be grouped into six categories: steroid hormones, metals, pesticides/biocides, polychlorinated biphenyls (PCBs), neuroactive drugs and others such as cyanobacterial toxins. Of them, steroid hormones are most relevant. Especially for progestins and glucocorticoids, circadian dysregulations were well demonstrated in fish and the underlying mechanism was supposed to be dependent on progesterone and glucocorticoid receptor signaling.

2. Circadian rhythms in zebrafish as representative vertebrate model organism

An endogenous circadian clock exists in organisms ranging from prokaryotes to humans, of which, mechanisms have been described comprehensively in mammals (Rutter et al., 2002; Mohawk et al., 2012). Although the basic principles of circadian function are likely to be the same in mammals and fish, as the core clock genes are largely conserved (Dunlap, 1998), the products of *clocks* in fish might have more functional diversities due to the genome-wide gene duplication events during evolution. Fish normally have more circadian genes than mammals, and thus, sub-functionalization and neo-functionalization of gene duplicates (paralogues) would occur (Vatine et al., 2011; Toloza-Villalobos et al., 2015). Circadian genes have been extensively identified in zebrafish, but also in Atlantic cod (*Gadus morhua*), rainbow trout (*Oncorhynchus mykiss*) and several other teleost fish (Davie et al., 2011; Vatine et al., 2011; Lazado et al., 2014; Betancor et al., 2014; Toloza-Villalobos et al., 2015; Zhao et al., 2016). Of them, most research on circadian disruption have been conducted in zebrafish. Thus, here we focus on zebrafish but also consider the circadian rhythm network of other fish species and mammals.

Our homologous alignments performed in zebrafish based on Ensembl GRCz11 database identified 43 circadian genes (supplementary material, Table S1). As shown in Fig. 1, its circadian molecular network with known specific functions mainly includes six groups of genes: *clock, arntl, per, cry, nr1d* and *ror*. These circadian genes constitute a circadian molecular network that includes a core heterodimer (*clock/arntl*) and several negative/positive feedback loops (Fig. 1). They act together and play a pivotal role in clock outputs and in physiological outcomes (Vatine et al., 2011). The positive element heterodimer and the negative elements, period (*per*) and cryptochrome (*cry*) genes, together form the core transcription-translation feedback loop (Vatine et al., 2011). The heterodimer proteins bind in the promoters of *per* and *cry* genes to induce their transcription, and the physical binding of Per and Cry proteins will interact to inhibit heterodimer transcription, thereby forming negative feedback regulation (Tamayo et al., 2015). In addition, nuclear receptor genes, *nr1ds* and *rors*, are also involved in the transcriptional transformation of heterodimers. The former is regulated by a negative and the latter by a positive feedback regulation mechanism (Ramakrishnan and Muscat, 2006). These six groups of genes constitute the core regulatory circuit of the circadian rhythm network, and their functions and regulation have been studied in detail (Vatine et al., 2011).

In addition, several additional genes involved in circadian rhythm regulation, including the extensively studied *nfil3, dbp, hlf, tef* and *dec*. Although identified, their mechanisms of action remain to be further explored. *Nfil3*, also known as *e4bp4*, encodes a basic leucine zipper transcription factor. *Nfil3-1* is conserved in vertebrates, while *nfil3-2* and *nfil3-3* are maintained in teleost fish but not in mammals (Sun et al., 2019). The gene product of *nfil3* contains DNA binding structures closely related to the *dbp*, *hlf*, and *tef* (PAR protein) products. Mammals usually have one *Tef* and one *Hlf* gene, but most teleost fish have two *tef* genes (*tefa* and *tefb*) and two *hlf* genes (*hlfa* and *hlfb*) (Carmona-Antoñanzas et al., 2017; Zhao et al., 2018; Sun et al., 2019). They seem to antagonize each other and complement each other in terms of the circadian oscillation mechanism, but the principle of interaction is unclear (Mitsui et al., 2001; Cowell, 2002). *Decs* encode proteins that belong to the basic helix-loop-helix protein superfamily. The products of *decs* suppress their own expression by competing with Clock/Arntl heterodimers for the DNA binding (Kato et al., 2014; Sato et al., 2018). *Dec1* and *dec2* of zebrafish have high sequence similarities with their mammalian counterparts, which inhibit the expression of *clock/arntl*. This feedback loop is interlocked with the feedback loop of *per* and *cry* (Abe et al., 2006).

3. Physiological processes regulated by circadian rhythms

A considerable proportion of non-clock genes are expressed in a circadian fashion. This has been shown from cyanobacteria up to mammals (Dvornyk et al., 2003; Gachon et al., 2004; Li et al., 2013). In promoters of many non-clock genes, which are regulated by circadian rhythms, E-boxes occur (Ripperger and Schibler, 2006). Via such target genes and their effects, central and peripheral circadian clocks directly regulate many aspects of physiological processes (Panda et al., 2002; Takahashi et al., 2008). Fig. 2 shows that different biological levels are concerned. Among them are metabolism, reproduction and behavior, which are particularly focused on in our review. All these processes can, in principle, be dysregulated by environmental chemicals (Matsuo et al., 2003; Fu et al., 2002; Huang et al., 2016).

3.1. Metabolism and detoxification

Circadian expression of components of nutrient metabolism (glucagon receptor, glucose transporters, carbohydrate metabolism), cholesterol biosynthesis and energy metabolism were observed in the liver of mammals and aquatic organisms (Panda et al., 2002; Paredes et al., 2014). Furthermore, circadian regulation of membrane transporters, transcripts of cytochrome P450s, phase II enzymes, as well as antioxidant enzymes were found (Li et al., 2013; Huang et al., 2016; Vera and Migaud, 2016; Lazado and Voldvik, 2020). Thus, xenobiotic

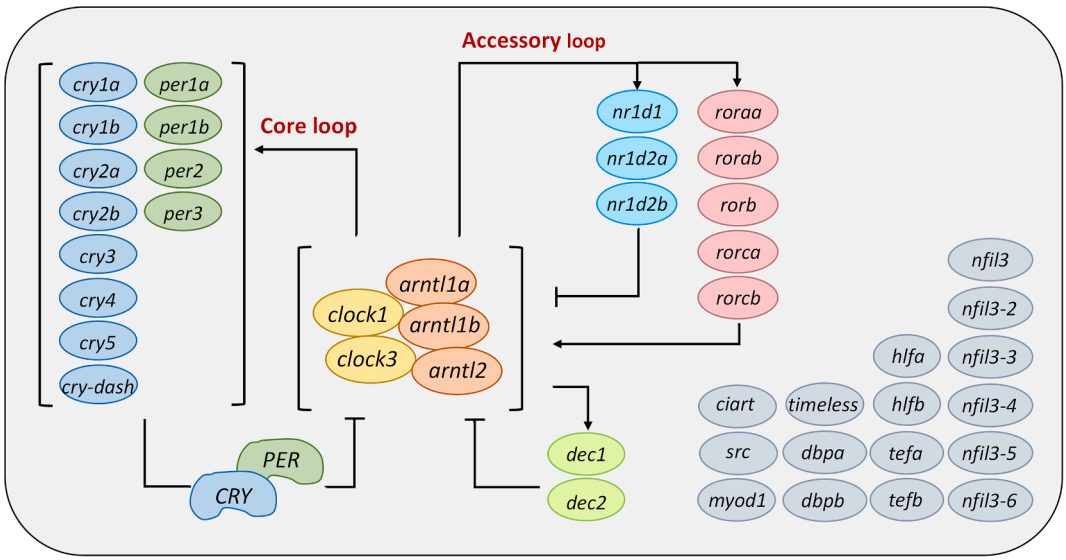

Fig. 1. Circadian rhythm system in zebrafish and associated genes in the core and accessory loops. Our homologous alignments (based on current zebrafish genome annotation (GRCz11) in Ensembl database) identified 43 circadian genes. Multiple paralogues exist in zebrafish owing to the evolutionary whole-genome duplication events. Full name of each gene is shown in the Supplementary Material in Table S1. The core component is the clock/arntl heterodimer, which binds in the promoters of *per* and *cry* genes to induce its transcription, and the physical binding of PER and CRY proteins will interact to inhibit clock/arntl heterodimer transcription, thereby forming a core negative feedback loop. Nuclear receptor genes, *nr1ds* and *rors*, are also involved in as accessory loops. The former is regulated by a negative and the latter by a positive feedback regulation mechanism. Circadian genes in grey color indicate that their mechanisms of action are not yet entirely understood.

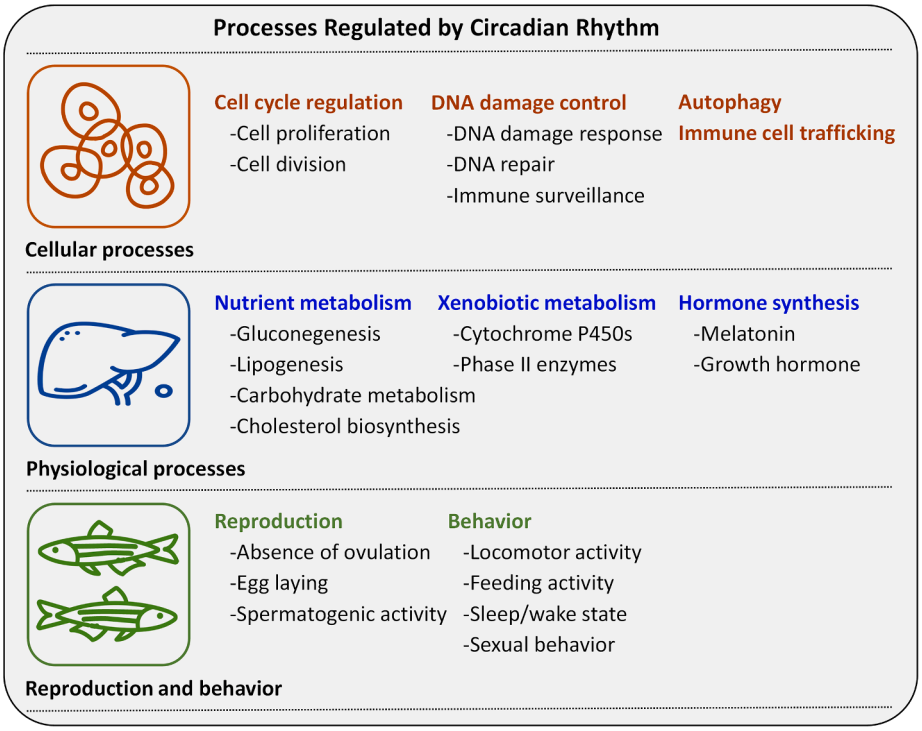

Fig. 2. Physiological processes at different levels of biological organization that are regulated by circadian rhythms. They can be affected by circadian disrupters.

metabolism is regulated by circadian rhythms, at least in part.

Genetic disruption of clock genes in mammals led to perturbation of metabolic functions of specific tissues, including intestine and liver (Bass and Takahashi, 2010; Cho et al., 2012). Circadian desynchrony, which occurs in humans (via shift-work, for example), can lead to metabolic pathologies, including obesity and diabetes (Buxton et al., 2012). Recently, limited information has been obtained on circadian regulation of metabolism in fish although multiple peripheral oscillators also occur. In the liver of rainbow trout (*Oncorhynchus mykiss*), circadian oscillation of clock genes was described, which was influenced by light and food (Stokkan et al., 2001). Rhythmic profiles of transcript abundance of enzymes related to carbohydrate and lipid metabolism were also described. They persisted in the absence of light/dark cycle and food availability (Hernandez-Perez et al., 2017). In Atlantic salmon (*Salmo salar*), daily rhythms were found in clock genes, lipid metabolism genes, as well as physiological stress (glucose, lactate and cortisol) and expression of antioxidant enzymes. This may affect the fish at multiple levels, such as growth that would be related to food intake, but also to

lipid metabolism and adaptive responses to the environment (Betancor et al., 2014; Vera and Migaud, 2016; Lazado and Voldvik, 2020).

The liver is a major site for biotransformation and detoxification of xenobiotics. Expression of transcription factors and xenobiotic metabolism enzymes showed circadian rhythmicity in zebrafish liver. Among them were transcripts encoding cyp1a and phase II enzymes gstr1 and sult2st2, as well as ABC transporters abcb4 and abcg2 (Carmona-Antoñanzas et al., 2017; Li et al., 2013; Zhao and Fent, 2016b). There is a link between circadian clocks and metabolism (Yang et al., 2006). Thus, besides xenobiotic detoxification by phase I and phase II enzymes, membrane transporters that play a role in diurnal transport of metabolites as well as nutrients are regulated by circadian rhythms.

3.2. Reproduction

Reproduction of animals including fish exhibits both daily and seasonal rhythms. Synchronous reproduction is important for reproductive success in animals. Presence or absence of ovulation, egg laying, spermatogenic activity, and sexual behavior show annual cycles and are influenced by light and temperature. Besides annual changes, daily variations occur in sex steroids in many fish (Lamba et al., 1983). Circadian rhythm also occurs in the expression of key genes involved in steroidogenesis (aromatase *cyp19a1a*), hormone production (*fhs*, *lh*), gonadal function and spawning behavior in zebrafish. In gonads, expression of aromatase, *dmrt1* and antimüllerian hormone (*amh*) were rhythmic, and in the brain, aromatase and *cyp11b* transcripts oscillated in males, while in ovary, expression of *roxl2* was rhythmic (Di Rosa et al., 2016).

Timing of reproduction and steroid production is controlled by the hypothalamic-pituitary-gonad (HPG) axis, which is necessary for many processes including gonad maturation, spawning and sex differentiation. Breeding takes place mostly during increasing (or sometimes decreasing) photoperiods in temperate regions and the pineal organ seems to be involved in mediating this effect, but details of the regulation are still open. In the grass puffer (*Takifugu alboplumbeus*), seasonal and daily oscillation in the transcription of genes encoding kisspeptin and gonadotropin inhibitory hormone and their receptor genes are regulated in the diencephalon by the circadian clock, melatonin and by temperature. They regulate the timing of spawning (Ando et al., 2018).

3.3. Behavior

Many organisms display either diurnal or nocturnal behavioral rhythms, including locomotor and feeding activity. The circadian clock enables animals to adapt in behavior to the day/light cycle. Thereby, light and temperature represent the key environmental timing cues (called Zeitgeber). In non-mammalian vertebrates, including zebrafish, melatonin biosynthesis takes place in both the retina and pineal gland (Falcon et al., 2007; Idda, et al., 2012). The fish pineal gland contains all elements required for photic entrainment and circadian rhythm generation. It is photoreceptive and contains an intrinsic circadian oscillator that drives melatonin synthesis rhythms, which is different from that of mammals (Vatine et al., 2011; Idda, et al., 2012). It then mediates the locomotor activity rhythm and sleep-like states and contributes to the regulation of several behaviors and physiological functions. Melatonin administration in fish induces a sleep-like state and diminishes locomotor activity and food intake. However, melatonin has multiple effects in fish neuroendocrine regulation, which is not completely understood (Falcon et al., 2007).

Circadian regulation of locomotor activity has been investigated in zebrafish (Hurd, et al., 1998; Cahill, et al., 1998; Cahill, 2002; Zhao, et al., 2018; Hu, et al., 2020). When zebrafish were maintained in a light-dark cycle, most activity was observed during daytime. When they were kept in constant conditions, circadian locomotor activity was observed for up to 10 days. Besides, the period of locomotor rhythm was temperature-compensated, varying little over the range of 18–28.5 °C, although it was longer in constant darkness than in constant dim light (Hurd, et al., 1998; Cahill, et al., 1998). In some activity records, two rhythmic components with different circadian periods were observed, suggesting that the regulation of activity occurred by two independent circadian oscillators (Cahill, 1996, 2002).

Furthermore, behavioral, physiological and molecular studies revealed that the visual system of zebrafish is also regulated by circadian clocks at multiple levels. This included the visual sensitivity as recorded by electroretinograms, synthesis of the hormone melatonin and expression of the *interphotoreceptor retinoid binding protein* gene and the core clock genes (Cahill, 1996; Rajendran et al., 1996; Li and Dowling, 1998, 2000; Guido et al., 2010).

Mutant *nr1d1* zebrafish larvae showed disrupted rhythms of locomotor activities. Under light-dark (LD) condition, *nr1d1* mutant fish displayed hyperactivity, which was similar to the phenotypes of zebrafish *per1b* null mutants. Under dark-dark (DD) conditions, *nr1d1* mutant fish showed a half-an-hour phase delay and a 0.25-h shortened period, which was similar to the phenomenon observed in mice, where the *Nr1d1* knockout mice display a 0.5-h shortened period under DD condition and also mania-like behaviors (Chung et al., 2014). Thus, *nr1d1* plays a conserved role in maintaining the locomotor activity rhythms (Huang et al., 2016).

4. Environmental factors affecting circadian rhythm regulation

4.1. Light, temperature and oxygen levels

Light-dark cycle is the primary environmental signal that synchronizes the circadian rhythm in a wide array of species, including fish (Brüning et al., 2015; Emery et al., 2000; Wang et al., 2020b). Besides, other environmental factors including temperature (Rensing and Ruoff, 2002; Lahiri et al., 2005; López-Olmeda et al., 2006) and oxygen levels (Mortola, 2007; Pelster and Egg, 2015) are of importance for regulating the circadian rhythm (Prokkola and Nikinmaa, 2018).

4.1.1. Light

Light-dark cycle is the key factor affecting the circadian rhythm of fish. Light exposure has a dramatic effect on the development and maintenance of self-sustained cellular clocks (Ralph and Mrosovsky, 1992). The major mechanism of the circadian system is the light-dependent production of melatonin by the pineal gland/organ, which is light-sensitive and directly processes photoperiodic information. It results in a circadian melatonin rhythm that provides periodic information for cells and organs, such as time of the day and season (Kulczykowska and Sánchez Vázquez, 2010; Brüning et al., 2015). Influence of artificial light at night on fish has been an area of interest with respect to aquaculture and ecotoxicology. Photoperiod manipulation has been successfully used to improve the growth and reproduction of a number of fish species, including Atlantic salmon (*Salmo salar*) (Adams and Thorpe, 1989; Thrush et al., 1994); haddock (*Melanogrammus aeglefinus*) (Trippel and Neil, 2003) and Nile tilapia (*Oreochromis niloticus*) (Wang et al., 2020b). However, artificial light can also have detrimental effects in nature. For instance, even very weak artificial light that illuminated the water at night had a strong impact on the rhythm of melatonin production in European perch. At high light intensity, the fish appeared to be completely deficient in any circadian melatonin rhythm (Brüning et al., 2015).

Recently, a genome wide transcriptomic analysis performed in larval zebrafish identified 2856 circadian oscillating genes responsive to light-dark cycles, which account for over 17% of all expressed genes. When their biological functions were annotated using KEGG databases, they are mostly enriched in the pathways related to circadian rhythm. Besides, components of the lysosome were enriched around Circadian Time 16 (CT16; CT0 is lights-on and CT14 is lights-off), proteasome components were enriched around CT20, and components involved in ribosome biogenesis were enriched around CT0 (Li et al., 2013).

Furthermore, transcriptional levels of *microphthalmia-associated transcription factor* (*mitfa*) were enriched. This gene product mediates circadian melanin synthesis. Additionally, altered circadian melanogenesis was observed that would lead to the changes in zebrafish skin color allowing zebrafish to adapt to its environment (Li et al., 2013).

Via a transgenic zebrafish line expressing a reporter protein driven by the promotor of *nr1d1*, *in vivo* circadian rhythms were monitored at a single cell level. The sequential initiation of the reporter expression was observed, starting at photoreceptors in the pineal gland, and subsequently spreading to cells in other brain regions. Even within the pineal gland/organ, heterogeneous onset of *nr1d1* expression was observed, in which each cell underwent circadian oscillation superimposed over a cell type–specific developmental trajectory (Wang et al., 2020a).

4.1.2. Temperature

Temperature is another important synchronizer that influences key aspects of the circadian clock. Temperature cycle is known as a strong entraining cue of circadian clocks that synchronizes circadian rhythms in most organisms, from bacteria to vertebrates (Rensing and Ruoff, 2002; Satralkar et al., 2007). The strongest zeitgeber effects in temperature were found in heterothermic animals, including lizards and dunnart (Evans, 1966; Francis and Coleman, 1990). Moreover, temperature pulses elicited phase response curves that were similar to those generated by light pulses (Barrett and Takahashi, 1995; Ruby et al., 1999). In fish, temperature cycles, even with a difference of only 2 °C between thermophase and cryophase, are demonstrated to synchronize the circadian expression of clock genes, which highlights the great sensitivity of fish the circadian rhythm system to small adjustments of temperature (Lahiri et al., 2005).

Temperature affected the developmental profile and overall levels of *per3* and *luc* mRNA in zebrafish larvae (Kaneko and Cahill, 2005). In the absence of light, exposure of fish embryos and primary cell lines to temperature cycles entrains circadian rhythms of clock gene expression. Temperature steps drive changes in the basal expression of certain clock genes in a gene-specific manner (Lahiri et al., 2005). Mechanistic studies have further demonstrated that temperature changes can directly affect the clock mechanism by accelerating or slowing component processes, as almost any process in a cell (Liu et al., 1998; Edery, 1999). Meanwhile, additional effects of temperature changes on the clock variables occur, for instance, through the second messengers cAMP and cGMP, or influences on the intracellular clock environment such as ion or metabolite concentrations (Rensing et al., 1995).

4.1.3. Oxygen level

A close interaction between hypoxia responses and the circadian clock has been widely revealed in many species (Mortola, 2007). Expression of *Hif-1α*, the hypoxic transcription factor, and several other downstream gene members of the hypoxic signaling pathway are tightly controlled by the circadian clock. The protein expressions follow a clear circadian rhythm under normal (normoxic) conditions in both zebrafish and mammals. Meanwhile, the amplitude of circadian cycles in turn is influenced by hypoxia itself (Egg et al., 2013; Adamovich et al., 2017; Sandbichler et al., 2018). Hypoxia has previously been described to alter circadian oscillations of physiological parameters including body temperature, metabolic rate, cortisol and melatonin levels by lowering their amplitudes (Seifert and Mortola, 2002; Bosco et al., 2003; Coste et al., 2004; Mortola, 2007; Touitou et al., 2010). Lowering of the oscillation amplitudes under hypoxia conditions were reported for expression of the *per1* gene in zebrafish larvae as well as in cultured cells (Egg et al. 2013). The reduced oscillations of *per1* gene transcripts were sustained even after 6 days of hypoxic treatment (Egg et al. 2014). A similar phenomenon was also observed for *per2* as well as *cry1* (Egg et al., 2013; Pelster and Egg, 2015).

The molecular mechanism responsible for these reductions can be assigned to the competitive binding of *hif-1α* to the same sequence (E-box region) in the promoter region of the clock genes *per1* and *per2*, as well as *cry1* to that bound by Clock. Thus, the circadian rhythm of *per* and *cry* transcription would be attenuated in hypoxic conditions (Egg et al., 2013; Pelster and Egg, 2015). The *Hif–Clock–Per* interactions have been clarified in mammals, which are also supposed to occur in fish (Chilov et al., 2001). In zebrafish, six hypoxic transcription factors can be identified, including *hif1a*, *hif1b*, *hif2a*, *hif2b*, *hif3a* and *hif3b* (Chilov et al., 2001). Cobalt chloride ($CoCl_2$) prevents Hif-1 protein degradation and has a similar effect to hypoxia conditions. There was a significant decrease in the amplitude of the *per1* transcript circadian oscillation in $CoCl_2$ treated zebrafish cells in a dose dependent manner under free-running conditions, further suggesting that Hif-1α protein was involved in hypoxia-induced decrease in *per* and *cry* promoter activities (Egg et al., 2013).

4.2. Redox balance and reactive oxygen species (ROS)

Redox status and circadian clock of cells are highly interconnected. The expression level and activity of antioxidant enzymes, including Sirt1 and Parp1, determine the levels of intracellular reactive oxygen species (ROS), which have been demonstrated to impinge on the expression patterns of circadian genes. Meanwhile, such antioxidant enzymes have been shown to follow a circadian pattern of expression, suggesting that the circadian system can regulate redox homeostasis in mammals (Stangherlin and Reddy, 2013). This highly synergistic relationship was thought to be caused by co-evolution (Hardeland et al., 2003). With the periodic changes of metabolism and external environment, ROS levels were also periodically increased in organisms. Meanwhile, a compensatory antioxidant rhythm was developed gradually to resist harmful oxidative stress (Milev and Reddy, 2015). Therefore, the destruction of redox balance is considered to be a crucial factor that is generating circadian disruption (Stangherlin and Reddy, 2013).

Redox signaling was proved to be competent to modulate *Per* transcript levels, and therefore, acute changes in redox balance can elicit phase-dependent circadian phase shifts in mammals (Putker et al., 2018). Studies on zebrafish have also proved that changes in redox state can actively control the expression of circadian genes. Treatment of light-responsive zebrafish Z3 cells with H_2O_2 triggers the induction of *per2* and *cry1a* gene transcripts. The induction kinetics and oscillation profile in response to H_2O_2 are identical to those initiated by light (Hirayama et al., 2007). This phenomenon has also been confirmed in other fish species. Atlantic salmon (*Salmo salar L.*) exposed to ROS oxidants showed a time-dependent stress response and affected the expression of core clock genes, including *per2* and *rev-erbα* (Vera and Migaud, 2016; Lazado and Voldvik, 2020).

As the underlying mechanism, NAD^+, the primary target of oxidative stress, plays an important role in modulating the functions of NAD^+-dependent enzymes, such as NAD^+-dependent protein deacetylase sirtuin-1 (Sirt1), and poly (ADP-ribose) polymerase 1 (Parp1), as well as the redox-sensitive transcription factor (Nrf2), which can directly control the transcriptional levels of circadian genes (e.g. *Rev-erb*) or indirectly regulate their posttranslational modifications (e.g. *Bmal1*, *Per2*) (Asher et al., 2008; Stangherlin and Reddy, 2013). Environmental compounds that target redox balance, such as copper oxide nanoparticles and climbazole, also affected biological circadian rhythms in this way (Vicario-Pares et al., 2018; Zhang et al., 2019).

There is a gap to be further explored in forthcoming studies: to experimentally verify, whether the genes that have been implicated to responses to chemical oxidants, are really directly controlled by circadian clock regulators. Knock-down or knockout experiments with selected clock-controlled genes related to adaptations and responses to environmental compounds can bring light into this question.

4.3. Environmental compounds

Besides natural environmental factors, anthropogenic impacts such as direct exposure of aquatic organisms to environmental contaminants,

or to cyanobacterial toxins that are promoted as a consequence of eutrophication and climate warming, were recognized as factors influencing circadian rhythms. Circadian perturbation following exposure to a range of environmental substances was demonstrated in a variety of aquatic organisms, especially in fish. Alterations were mainly shown on the transcription level and on behavioral alterations such as locomotor behavior. As shown in Fig. 3, and in more detail in Table S2, six major categories of environmental compounds have been identified as circadian disrupters so far. They belong to steroid hormones, metals, biocides and pesticides, polychlorinated biphenyls (PCBs), neuroactive drugs and other compounds such as cyanobacterial toxins and bisphenol A. In the following, we summarize current knowledge about their effects on the core circadian rhythm system, as well as to the related physiological outcomes. We also consider molecular mechanisms behind these effects, as far as they are known, but they are still far from being understood.

4.3.1. Steroid hormones

Glucocorticoids are essential for circadian cell cycle rhythmicity in mammals and fish (Dickmeis et al., 2007; Dickmeis, 2009). The diurnal release of these hormones is under control of the circadian clock. Production and secretion of glucocorticoids involves a central peacemaker in the hypothalamus and a circadian clock in the adrenal glands, where glucocorticoids are produced. The rhythmical release of hormones contributes to synchronization of the cell autonomous clocks in the body. The pituitary-adrenal axis plays an essential role in establishing these rhythms, as deduced from mutant zebrafish (Dickmeis et al., 2007). Mutants lacking corticotrope pituitary cells showed attenuated cell proliferation rhythms, while clock gene expression was not affected. Reduced cortisol levels in these mutant fish imply that glucocorticoids are components of the systemic signaling pathway needed for circadian cell cycle rhythmicity. Autonomous clock mechanisms in cells act together with systemic signaling in which glucocorticoids are essential. Consequently, this implies that alteration of endogenous levels and/or exposure to exogenous glucocorticoids affects the regulation of circadian rhythms and associated physiological pathways.

Recently, this phenomenon was demonstrated for several synthetic glucocorticoids such as dexamethasone and cortisol that caused alteration of locomotor behavior (Zhao et al., 2018; Zhao and Fent, 2016a) and gonad histology (Faltermann et al., 2020). The circadian rhythm network of the brain of zebrafish exposed to fludrocortisone showed significant changes, of which transcriptional up-regulation of *per1a* and *nr1d1* were the most obvious ones. Exposure also resulted in premature hatching of zebrafish embryos, acceleration of development of F1 embryos, and altered larval swimming behavior (Zhao et al., 2016). Exposure to fluticasone propionate and glucocorticoid mixtures with triamcinolone caused transcriptional up-regulation of the circadian genes *nr1d1* and *per1a* in zebrafish larvae, which were more pronounced at high concentrations. Related transcripts of genes encoding enzymes of glucose metabolism (*pepck1*) and genes encoding proteins involved in tissue growth and repair (*mmp-9* and *mmp-13*) were also significantly up-regulated (Willi et al., 2019).

The molecular mechanisms for the induced transcriptional levels of circadian genes upon glucocorticoids exposure are not yet fully understood, while the glucocorticoid receptor (GR) was demonstrated to be required for such regulation in some studies (Rubel et al., 2012; Yamamoto et al., 2005). A glucocorticoid response element (GRE) binding domain was discovered to exist in clock gene promoter regions in mice (Bass, 2012), and in zebrafish and goldfish (Sanchez-Bretano et al., 2016; Zhao et al., 2018). It was demonstrated to be necessary for glucocorticoid signaling to cause a rapid increase in *Per1* mRNA levels

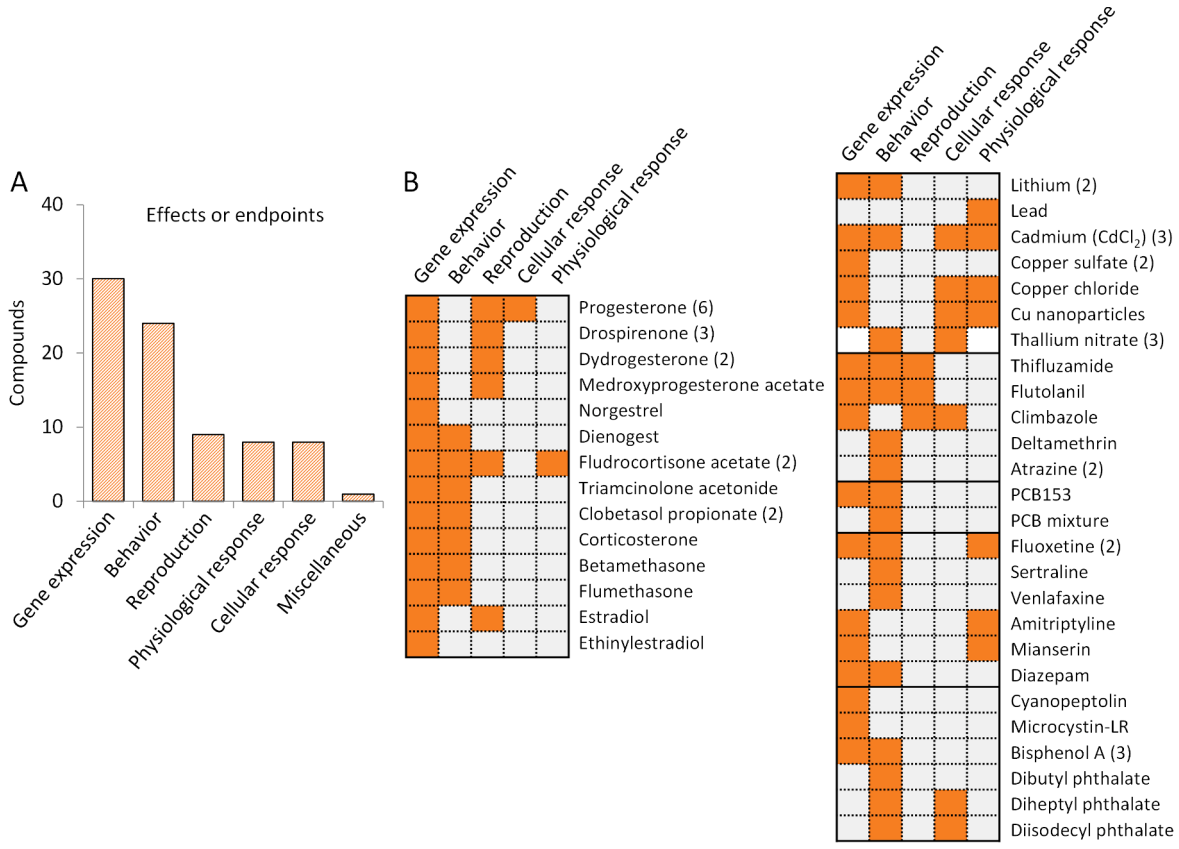

Fig. 3. Summary of circadian related effects assessed in environmental chemicals. (A) Number of chemicals with circadian gene changes at different effect levels. Categories are gene expression or cellular, physiological, reproductive and behavioral effects. (B) Details of reported effects on the endpoints for each circadian disrupter, grouped in steroid hormones and other compounds. The summary of effects for each compound derived from different studies (number of studies given in parenthesis) is shown. More information is shown in Table 1 and Table S2.

(Bass, 2012; Zhao et al., 2018). GR was shown to be important for the regulation of behavioral activity and rhythmic alterations of melatonin concentrations but plays a minor role in the regulation of rhythmicity of clock-related gene expressions. Thus, a mechanism for *gr* functionality at the transcriptional level could not be explained (Jaikumar et al., 2020). Impairment of food entrainment on locomotor activity was observed in *gr* knockout zebrafish larvae and adults but the molecular background of this behavioral phenomenon, such as changes in clock gene expressions, was not identified (Morbiato et al., 2019).

Circadian disruptive effects for another major group of steroid hormones, the progestins, have also been extensively studied. When adult zebrafish were exposed to progesterone for 14 days, expression of core circadian genes including *nr1d2b* and *per1b* were remarkably down-regulated in the zebrafish brain, meanwhile, *nr1d1* was significantly down-regulated in the ovary (Zucchi et al., 2013). Transcriptional alterations were further observed for cell cycle regulation, apoptosis and reproduction related genes such as *zona pellucida 3* (*zp3*) and *vitellogenin*, suggesting potential influence of progesterone on the HPG axis and steroid hormone synthesis (Zucchi et al., 2014). Furthermore, strong positive correlations between transcriptional levels of circadian genes and HPG and liver axis genes were observed (Zhao and Fent, 2016a; Zucchi et al., 2013). Exposure of zebrafish to synthetic progestins drospirenone, dydrogesterone (DDG) and medroxyprogesterone acetate (MPA) also resulted in dose-dependent transcriptional alterations of *nr1d1*, *per1b* and *cry2b* in the zebrafish brain, as well as in eyes. Transcript of genes involved in steroid hormone receptor activities were enriched as well (Zhao et al., 2015; Zhao and Fent, 2016a; Zucchi et al., 2014).

Natural and synthetic estrogens also affected circadian rhythm systems in fish. Exposure of zebrafish to estradiol led to a slight expressional up-regulation of circadian genes (*clock*, *arntl* and *nr1d1*), as well as changes of HPG axis-related gene transcripts (Liang et al., 2019). Estradiol but not its metabolites (estriol, estrone) led to transcriptional up-regulation of key genes at certain times, while ethinyl estradiol led to transcriptional down regulation of genes such as *per1a* and others (Zhao et al., 2018). However, all estrogens increased locomotor activity of larvae. A mixture of ethinyl estradiol and norgestrel significantly induced the transcription of *cry1a*, *cry2a*, *cry2b*, *per3*, *arntl1b*, *arntl1* and *clock1a* genes, and simultaneously, inhibited the expression of *cry3* and *cry4*. This mixture also posed a risk to fish reproduction (Liang et al., 2017). A comparison of 20 steroids of the progestin, glucocorticoid, estrogen and androgen class showed that glucocorticoids were most effective and only androgens ineffective for transcriptional and behavioral changes (Zhao et al., 2018).

4.3.2. Metals

Metals, especially transition metals, are another major group of environmental circadian disrupters. The first report was generated in 1981, where lithium was identified to alter the circadian rhythm in goldfish (*Carassius auratus*) (Table S3). Long-term (30 days) lithium treatment slowed down and disrupted circadian locomotor activity rhythms in goldfish (Kavaliers, 1981), which was similar to effects reported in mammals (Kafka et al., 1982). In zebrafish, lithium exposure led to significant up-regulation of circadian genes *clock1a* and *bmal1b*. The expression levels of *per1b* and *per2* were up-regulated as well and this change was related to the acute stress response. Besides, lithium affected physiological processes including the expressions of neuropeptide Y and melatonin receptors and intermitted hypoxia/reoxygenation. Adverse effects on tissue development and regeneration also occurred (Xiao et al., 2017). In a transgenic zebrafish line, Tg (4xE-box: Luc), expressing a luciferase reporter gene under the regulation of four E-boxes, a period expansion of 0.7 h was observed upon lithium chloride treatment. Reporter gene mRNA expression was also detected in the adult brain and revealed differential clock activity across the brain, overlapping with endogenous clock gene expression. Core clock activity was strongly correlated with brain regions, where neurogenesis takes place (ventral and dorsal telencephalon, preoptic area, hypothalamus), and it was detected in several types of neural progenitor cells (Weger et al., 2013).

Waterborne copper exposure also disrupted circadian rhythm. When zebrafish were exposed to copper for three days, expression of *per1* and *cry1a* in the brain and liver lost rhythm, and the peak appearance time was significantly delayed at concentrations of 25 μg/L and above. Furthermore, daily oscillations of superoxide dismutase and catalase enzymatic activity were dysregulated, suggesting their correlation both with clock genes (*per1*, *per2*, and *cry1a*) and the organism's energy costs (Doria et al., 2018). Besides, adult zebrafish exposed to environmental concentrations of copper oxide nanoparticles displayed time-dependent circadian rhythm dysregulations, which was consistent with results for ionic copper exposure. The circadian genes *per2*, *cry2a* and *cry5* showed significant up-regulation, and additionally, effects on cell growth, DNA repair, oxidative stress and metabolic processes were observed (Vicario-Pares et al., 2018). Similar phenomena also occurred in red seabream (*Pagrus major*) (Kim et al., 2017).

Cadmium has also been identified as a circadian disrupter. Zebrafish larvae exposed to very high concentrations of cadmium chloride (5 ppm) displayed altered transcript levels of *clock1a*, *bmal1b* and *per2*, all with significant up-regulation during the light phase. Metabolic processes, such as proteolysis and amino acid metabolism and autophagy were further affected. These circadian rhythm disruptive effects were suggested to be activated via immune response and some G protein-coupled receptors (Xiao et al., 2016). Furthermore, disrupted circadian behavior (behavior strength) and metabolism responses (oxygen consumption) in zebrafish were observed by use of a novel online monitoring systems (Qi et al., 2017; Yang et al., 2018). For instance, after cadmium chloride exposure (5 μg/L) for 6 days, zebrafish larvae showed significant changes in behavior strength and circadian rhythm (in the aspect of periodicity) with a clear time delay (1-hour delay) (Yang et al., 2018).

Lead (Pb) also affected circadian rhythm in fish at 1 mg/L. Waterborne lead exposure for 28 days caused circadian variations of various neurotransmitters in fathead minnow (*Pimephales promelas)* brain, including norepinephrine, vanillylmandelic acid, homovanillic acid and hydroxy indoleacetic acid (Spieler et al., 1995).

4.3.3. Pesticides and biocides

Currently, only a few pesticides were investigated for circadian rhythm disruption. Thifluzamide, a succinate dehydrogenase inhibitor, is a widely employed fungicide for preventing and treating diseases in rice. Treatment of zebrafish embryos with thifluzamide for four days altered mRNA levels of core clock genes including *clock1a*, *clock2*, *bmal1a* and *bmal2*, and genes of the *per* and *cry* family with dose-related effects for *cry1ba* and *clock1*, and significant induction of *cry1ba* and *cry1bb* at 0.19 mg/L and higher. Growth hormone and dopamine levels were significantly lowered and mRNA levels of genes related to zebrafish development (*gh*, *igf*, *bmp4*, *lox* and *he1a*), behavior (*mao* and *dbh*) and steroid hormone synthesis (*cyp19*, *dmrt1*, *3β-hsd* and *17β-hsd*) were significantly changed, which was consistent with inhibition of embryonic development and swimming behavior. It is suggested that these effects are primarily attributed to increase in *clock1a* expression, which might be, at least partly, responsible for fish abnormal development and behavior (Yang et al., 2019a).

Similarly, zebrafish embryos exposed to flutolanil, another fungicide that is used for controlling bunt and smut diseases of cereals, for four days, significantly inhibited the expression of positive clock genes (*clock1a*, *bmal1a*, *bmal1b*, *bmal2*, and *aanat2*) and negative clock genes (*per1b*, *cy1aa*, *cry1ab*, *cry1ba* and *cry1bb*) at 0.125–2 mg/L. In addition, flutolanil exposure led to significant increases of melatonin and decrease of growth hormone levels at 2.0 mg/L, which was consistent with the abnormal embryonic development and spontaneous movements observed (Yang et al., 2019b).

Climbazole is an antifungal active ingredient used in personal care products. After exposure of zebrafish to climbazole, transcription of

several core circadian genes was altered, such as down-regulation of *cry1a* at very low concentrations of 100 ng/L and of *clockα*, *arntl2*, *nr1d1*, *nr1d2a* and *nr1d2b* at 10 μg/L. Of the redox system, genes encoding uncoupling protein 2 (*ucp2*) and B-cell lymphoma 2 (*bcl2*), which are associated with reactive oxygen species, were also down-regulated. In addition, transcripts of *mprα* encoding the membrane progesterone receptor protein that plays a key role in induction of oocyte maturation was down-regulated. The hydroxysteroid dehydrogenase genes (*hsd3b1*, *hsd11b2*, and *hsd17b3*) associated with steroid synthesis were dysregulated by clenbuterol, which caused irreversible virilization in zebrafish (Zhang et al., 2019).

Another pesticide that displayed circadian disruption in fish was the herbicide atrazine. It is considered as an endocrine disrupter, increases lipid peroxidation and disrupts liver metabolism (Nwani et al., 2010). After exposure to 0.003 mg/L for six days, the average behavioral intensity of goldfish showed a significant decrease, and the switching pattern of the circadian rhythm phase changed (Yang et al., 2018). In zebrafish, the exercise intensity was weakened, and the periodicity of the circadian rhythm showed a significant 1-hour delay under atrazine exposure (Yang et al., 2018).

4.3.4. Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are a legacy of industrial production and use and represent highly persistent and ubiquitous environmental pollutants. They have been shown to be cancerogenic, immunotoxic, neurotoxic and cause metabolic disorders and developmental effects. While effects of coplanar PCB congeners that act by interaction with the aryl hydrocarbon receptor (AhR) are well known, non-coplanar PCBs are less studied but were shown to be neurotoxic and affect metabolism, endocrine and immune function. Recently, an important non-coplanar PCB congener was demonstrated to interfere with circadian rhythm regulation. Exposure of PCB153 led to significant transcriptional up-regulation of core clock genes, including cryptochrome (*cry1aa*, *cry1ab*, and *cry1bb*), period (*per1a*, *per1b*, *per2*, and *per3*), *rorcb* and *nr1d1*genes in zebrafish embryos. Especially, all paralogs of *period* and 2 out of 3 *cryptochrome* genes were up-regulated at 0.1, 1 and 10 μM. In addition, transcriptional disruption of circadian rhythms had been associated with dysfunction of numerous physiological processes including apoptosis, cell cycle, metabolism and circadian behavior (Aluru et al., 2020). Exposure of adult zebrafish to PCB mixtures led to a significant increase in swimming activity at the end of the night, which was suggested to be circadian rhythm regulated and triggered via AhR mediated response (Pean et al., 2013).

Similar phenomena were observed in mammals. The rhythmic expression of core clock genes (*Bmal1*, *Clock*, *Cry1*, and *Per2*) and CCGs (*Rev-evbα* and *Rev-evbβ*) were dysregulated in the liver of mice, which were exposed to a low dose (0.1 mg/kg body weight) of coplanar PCB126 for 4 weeks. In addition, PCB126 caused accumulation of glucose and cholesterol levels and caused liver damage by impairing the circadian rhythm (Shen et al., 2019). In adult male Wistar rats treated with the polyhydroxy biphenyl hydroxylated metabolite 4-hydroxy-2,3,3′,4′, 5-pentachlorobiphenyl (4-OH-PCB107) at concentrations of 170 ng/kg and above, the circadian genes *Nr1d1*, *Nr1d2* and *Tenc1* were up-regulated and *Arntl* and *Cry1* significantly down-regulated. Furthermore, liver damage and changes in the expression levels of metabolism-related genes occurred in a dose-dependent manner (Ochiai et al., 2018). Thus, it seems that PCBs induce metabolic and behavioral alterations via circadian rhythm dysregulation in fish and mammals.

4.3.5. Neuroactive drugs: Antidepressants and sedatives

Neuroactive drugs, especially antidepressants, affected the swimming behavior of aquatic organisms, and this effect was supposed to be related to circadian rhythm dysregulation. Such drug residues occur in hospital and municipal wastewaters. The body's rhythmic functions including neuroendocrine rhythm such as hormone secretion are regulated by a coordinated network of central and peripheral circadian pacemakers. Thus, dysregulation of the circadian rhythm system often results in adverse outcomes in the circadian activity patterns (Urbanski, 2011).

Male mosquitofish (*Gambusia affinis*) exposed to the mixture of antidepressant drugs venlafaxine, fluoxetine and sertraline showed a significant change in diurnal activity patterns at low concentrations (1 μg/L). When male mosquitofish exposed to 100 μg/L venlafaxine alone for a week, the average daytime activity decreased significantly. These neuroactive drugs act on neuroendocrine-mediated pathways in vertebrates, such as the reproductive hormones homeostasis (Menningen et al., 2008; Melnyk-Lamont et al., 2014; Parrott and Metcalfe, 2017). The circadian rhythm is well known to be directly controlled by the neuroendocrine system (Urbanski, 2011). Thus, the pattern of influence on daily activity is consistent with the known mechanism of action of these compounds on the neuroendocrine pathways (Melvin, 2017).

At the transcriptional level, zebrafish circadian genes *per2* and *nr1d1* were significantly down-regulated after treatment with antidepressants amitriptyline, fluoxetine and mianserin at environmentally relevant concentration (0.1 μg/L), of which the effect of mianserin was most significant (Wu et al., 2017). This alteration is consistent with previous reports that antidepressants can rapidly ease depression by changing the abnormal clock gene expression to achieve a sleep deprivation therapy (Bunney and Bunney, 2013). In addition, transcripts of *cyp2k6*, a gene encoding cytochrome P450 enzyme that is involved in the metabolic process, were significant down-regulated (Wu et al., 2017).

Diazepam, a benzodiazepine used to treat anxiety, alcohol withdrawal and seizures, is a well-known drug. Transcriptome analysis in zebrafish demonstrated transcriptional alteration of genes involved in rhythmic processes, especially in the circadian rhythm, in adult zebrafish exposed to diazepam at environmentally relevant concentrations (Oggier et al., 2010). In the male zebrafish brain, expression of genes of the ARNTL family (*arntl1a*, *arntl1b*, and *arntl2*), rev-erb receptors (*nr1d4a* and *nr1d4b*), and *rorcb* genes appeared to be significantly up-regulated. Transcripts of period family members (*per1*, *per2*, *per3*, and *per4*) were significantly down-regulated and those of cryptochrome family members (*cry1b*, *cry2b*, *cry3*, *cry4*, *cry5* and *cry-dash*) changed to varying degrees. Especially transcriptional alteration of *nr1d4b* was most prominent with a significant increase of up to 10.5 times (log2). Similar effects were revealed in zebrafish embryos. Furthermore, exposure to diazepam altered locomotor behavior. Even low doses resulted in overactive embryonic swimming behavior, which showed that dysregulation of circadian rhythm gene expression mediates behavioral alterations at environmental concentrations (Oggier et al., 2010).

4.3.6. Other environmental substances

4.3.6.1. Cyanobacterial toxins. Microcystins such as MC-LR produced by cyanobacteria exhibit adverse effects on liver biorhythm regulation and metabolic processes. They are produced during the outbreak of cyanobacteria blooms and threaten aquatic organisms and human health (via drinking water consumption). Hepatic transcriptome analysis revealed that the circadian rhythm signaling was the most affected pathway in both female and male medaka fish after exposure to 5 μg/L MC-LR for 28 days, evidenced by significant down-regulation of *per* and *cry* gene families accompanied by expressional up-regulation of *bmal*. Furthermore, various metabolic pathways, such as amino acid metabolism, lipid metabolism and energy production, were disturbed. A notable decrease in vitellogenin and choriogenin protein levels were further observed, which was consistent with adverse effects on fecundity and egg hatchability. The observed hepatic circadian perturbation was suggested to be, at least partially, responsible for the hepatic alterations and the reproductive disturbance (Qiao et al., 2016).

Another cyanobacterial toxin affecting circadian rhythm regulation is cyanopeptolin CP1020, which is produced by *Microcystis* and

Planktothrix strains. Transcriptome analysis of zebrafish exposed to CP1020 identified the most significantly affected pathways including circadian rhythm, DNA damage and repair and response to light. The expression of *nr1d1*, *per1a* and *cry5* was down-regulated when zebrafish larvae were exposed to 100 μg/L and 1000 μg/L of CP1020 for 4 days. Among them, strongest changes were observed for the *nr1d1* transcript. In addition, transcripts of other genes including *xpc* and *ddb2* that are involved in DNA damage recognition and repair were remarkably down-regulated (Faltermann et al., 2014).

4.3.6.2. Organic chemicals. The estrogenic chemical bisphenol A (BPA) was identified to alter the expression of circadian genes. After BPA exposure, the expression of core circadian genes *per2* and *cry1* was significantly down-regulated in goldfish brain and liver (Choi et al., 2017). BPA exposure also reduced attacking behavior of male zebrafish (Weber et al., 2015). In killifish (*Fundulus heteroclitus*), BPA exposure led to expressional dysregulation of the core clock genes and caused the asynchrony of *clock*, *per2*, *cry1* and *bmal1* expression (Rhee et al., 2014).

Another type of environmental chemicals that displayed circadian disruption in fish are phthalates, which are widely used as plasticizers. These compounds show reproductive toxicity and could affect lipid peroxidation in fish (Nwani et al., 2010). After six days of exposure to dibuty phthalate (DBP) at concentration of 3 μg/L, the behavioral strength of goldfish in the dark was significantly reduced. The biological rhythm of behavioral strength became weaker, and the fluctuation of day and night activities was remarkably reduced (Ren et al., 2019). Similar phenomena also occurred for diheptyl phthalate (DHpP) and diisodecyl phthalate (DIDP). The significantly reduced swimming strength after a 15-days exposure to DHpP and DIDP was observed in adult zebrafish (Poopal et al., 2020). However, these few observations should be followed by more detailed investigations to clearly confirm whether phthalates really act as circadian disrupters.

5. Knowledge about and implications for human exposure

Compared to health implications of disrupted temporal sleep and feeding pattern, very little is known about effects of environmental chemicals acting as circadian disrupters in animals and humans. The lack of knowledge is more extensive than in fish. In medicine, the side effect of therapeutic use of glucocorticoids, which affect circadian rhythm and sleep, is known for a long time. In addition, lithium, diazepam and antidepressants (i.e. fluoxetine) used in psychiatry to treat disorders are known for such side effects; lithium has already in 1982 been shown to have an effect on circadian neurotransmitter receptor rhythm (Kafka et al., 1982). However, implications of metals on circadian rhythm are little known, with the exception of cadmium (Jiménez-Ortega et al., 2012). Diurnal variations were observed in the sensitivity to and toxicity of several metals, but also pharmaceuticals and other organic chemicals. The circadian clock can alter drug and xenobiotic metabolism (via activity of drug metabolizing enzymes), and therefore, efficacy and side effects of drugs can vary depending on the time of administration.

However, current knowledge about chemicals interfering with regulation of circadian rhythm in humans and mammals is very restricted. Currently, there is a vast gap of knowledge on this molecular and physiological endpoint and most knowledge has been obtained from zebrafish. Table S3 summarizes the 22 22 compounds that interfere with circadian rhythm regulation in mammals.

Among the most prominent environmental compounds are AhR activating compounds, including 2,4,7,8-TCDD, Aroclor 1221, PCB126 and benzo[a]pyrene. Although not specifically assessed in mammals, many effects of environmental pollutants may be related to dysregulation of circadian rhythms with disruption in cellular metabolism, leading to metabolic, immune and reproductive effects. These effects may have been noted but not related to circadian rhythm dysregulation.

Furthermore, effects have been assessed in zebrafish as a model organism and can be translated to mammals and humans. For instance, the non-ortho PCB153, which disrupts circadian rhythm in zebrafish (Aluru et al., 2020), causes transcriptional changes in many physiological processes that ultimately result in the observed adverse effects of this PCB congener in mammals. A hydroxy metabolite of PCB (4-OH-pentachlorobiphenyl) is another PCB related compound that affected expression of genes involved in circadian rhythm in rats (Ochiai et al., 2018). These and other data indicate that experimental knowledge obtained with zebrafish or another model organism can be extrapolated to effects of circadian disruption in human physiology and behavior. This is based on the fact that underlying mechanisms and mode of actions are similar if not identical at least in basic principles.

Among the few additional environmental compounds earlier shown to affect circadian rhythm in mammals is methylmercury (Arito et al., 1983). Dichloromethane (Andersen et al., 2017) and acrylamide (Tan et al., 2018) were recently shown to alter the expression of clock genes, and the fungicide tolylfluanid, to alter behavior (Regnier et al., 2015).

Together, the current state of knowledge is surprisingly limited. Currently, it is open whether, how and to what extent environmental chemicals affect circadian rhythm regulation in mammals and humans. This potential adverse outcome pathway has not, or very rarely, been assessed in toxicology and medical science. Therefore, there is an urgent need to consider this endpoint in the assessment of chemicals/drugs and of environmental contaminants. Furthermore, there is also a need to develop biomarkers to assess circadian function by molecular, cellular or physiological signals to identify this adverse outcome pathway in the toxicological assessment of chemicals.

6. Conclusions and needed research

Dysregulation of circadian rhythms can impact numerous aspects ranging from cellular processes to reproduction and behavior. This is known for changes of light-dark cycles and environmental factors such as temperature and oxygen levels. Less is known about anthropogenically derived environmental chemicals that act as circadian disrupters. This came into light only recently (Faltermann et al., 2014; Xiao et al., 2016; Doria et al., 2018; Yang et al., 2018; Prokkola and Nikinmaa, 2018; Willi et al., 2019; Aluru et al., 2020).

Here, we identified 40 environmental compounds that interfere with circadian rhythms in fish, of which steroid hormones are most relevant (Table 1). Fig. 3 shows that for 30 compounds, determined endpoints were transcriptional alterations of circadian genes. For 24 compounds, behavioral changes such as locomotor activity (swimming behavior) or social behavior were assessed. Reproduction was assessed for 9 compounds (steroid hormones, pesticides/biocides), while other physiological effects were assessed for only a few compounds (Table S2).

Most studies demonstrated transcriptional alterations of core circadian rhythm genes by environmental chemicals. However, the link between these alterations to physiological outcomes is not well established. This open gap should be filled in forthcoming studies. Furthermore, most studies determined transcriptional and behavioral alterations, often as an isolated parameter, but other endpoints, particularly metabolic outcomes, cell proliferation and development have little been studied. There is a need to focus on these endpoints besides transcriptional and behavioral alterations.

Research of circadian disruptions would be further and greatly benefit from the availability of new technologies, such as large-scale Omics analysis (transcriptomics, proteomics and metabolomics) (Wang et al., 2009; Li et al., 2013), molecular genetic techniques (knock-in and knock-out strategies) (Hirao et al., 2010; Cho et al., 2012), transgenic vertebrates (Kaneko and Cahill, 2005; Wang et al., 2020a) and even the integration of multidisciplinary approaches (Agostinelli et al., 2016; Ma et al., 2019), which are beyond the traditional transcriptional analysis performed by qRT-PCR and WISH, and behavior alterations measured via video-tracking systems.

Table 1
Environmental chemicals affecting circadian rhythm regulation in fish.

Category	Compound	Fish species	Life stage	Duration of exposure	LOEC	Effect, endpoint	Reference
Steriod hormones	Progesterone	Zebrafish	Adult	14 d	3.5 ng/L	Gene expression; Cell cycle; Reproduction	Zucchi et al., 2013
	Progesterone	Carp	Juvenile	10 d	5 ng/L	Gene expression; Reproduction	Xia et al., 2019
	Progesterone and Drospirenone	Zebrafish	Adult	14 d	50 + 4 ng/L	Gene expression; Reproduction	Zucchi et al., 2014
	Progesterone and Drospirenone	Zebrafish	Adult	21 d	7 ng/L	Gene expression; Reproduction	Zhao et al., 2015
	Progesterone and Drospirenone	Zebrafish	Adult	21 d	7 ng/L, 99 ng/L	Gene expression	Zhao et al., 2016
	Estradiol and Progesterone	Zebrafish	Larvae	4 d	5000 ng/L	Gene expression; Reproduction	Liang et al., 2019
	Medroxyprogesterone acetate and Dydrogesterone	Zebrafish	Larvae, adult	144 h, 21 d	5 ng/L, 50 ng/L	Gene expression; Reproduction	Zhao et al., 2015
	Fludrocortisone acetate	Zebrafish	Adult	21 d	6 ng/L	Gene expression; Reproduction; Swimming behavior; Metabolism	Zhao et al., 2016
	Ethinylestradiol and Norgestrel	Zebrafish	Larvae	4 d	50 ng/L, 50 ng/L	Gene expression	Liang et al., 2017
	Fluticasone propionate, Triamcinolone acetonide and Clobetasol propionate	Zebrafish	Larvae	5 d	0.98 μg/L	Gene expression; Swimming behavior	Willi et al., 2019
	Dydrogesterone	Zebrafish	Larvae	140 h	3.39 ng/L	Gene expression	Shi et al., 2019
	Corticosterone, Betamethasone and Flumethasone	Zebrafish	Larvae	5 d	0.1,1 μg/L	Gene expression; Swimming behavior	Willi et al., 2019
	Clobetasol propionate	Zebrafish	Larvae	5 d	10 ng/L	Gene expression; Swimming behavior	Willi et al., 2018
	Dienogest	Zebrafish	Larvae	6 d	0.01 μg/L	Gene expression; Locomotor activity	Schmid et al., 2020
Metals	Lithium	Goldfish	Adult	10 d	104 mg/L	Locomotor activity; Social behavior	Kavaliers, 1981
	Lithium	Zebrafish	Larvae	97 h	250 mg/L	Gene expression	Xiao et al., 2017
	Lead	Fathead minnows	Adult	28 d	1000 μg/L	Neurotransmitter levels	Spieler et al., 1995
	Cadmium ($CdCl_2$)	Zebrafish	Larvae	1 d	5 mg/L	Gene expression; Autophagy; Metabolism;	Xiao et al., 2016
	Cadmium ($CdCl_2$)	Zebrafish	Adult	2 d	4.26 mg/L; 42.6 mg/L; 85.2 mg/L	Swimming behavior; Metabolism	Qi et al., 2017
	Cadmium ($CdCl_2$)	Zebrafish	Adult	6 d	5 μg/L	Swimming behavior	Yang et al., 2018
	Copper sulfate	Red seabream	Adult	36 h	30 μg/L	Circadian rhythm proteins in blood plasma	Kim et al., 2017
	Copper chloride, Cu nanoparticles	Zebrafish	Adult	3 d, 21 d, 180 d	10 μg/L	Gene expression; Metabolism; Oxidative stress	Vicario-Pares et al., 2018
	Copper sulfate	Zebrafish	Adult	3 d	5 μg/L	Gene expression	Doria et al., 2018
	Thallium nitrate ($TlNO_3$)	Zebrafish	Adult	15 d	0.1 μg/L	Metabolism	Ma et al., 2019; Li et al., 2020
	Thallium nitrate ($TlNO_3$)	Zebrafish	Adult	15 d	0.1 μg/L	Swimming behavior	Zhao et al., 2020
Pesticides and biocides	Thifluzamide	Zebrafish	Larvae	4 d	190 μg/L	Gene expression; Reproduction; Swimming behavior	Yang et al., 2019a,b
	Flutolanil	Zebrafish	Larvae	4 d	125 μg/L	Gene expression; Reproduction; Swimming behavior	Yang et al., 2019a,b
	Climbazole	Zebrafish	Larvae	2 d, 7 d, 14 d	0.1 μg/L	Gene expression; Oxidative stress; Reproduction	Zhang et al., 2019
	Atrazine	Goldfish	Adult	6 d	3 μg/L	Swimming behavior	Ren et al., 2019
	Atrazine	Zebrafish	Adult	15 d	3 μg/L, 30 μg/L	Swimming behavior	Zhao et al., 2020
	Deltamethrin	Zebrafish	Adult	15 d	2 μg/L, 20 μg/L	Swimming behavior	Zhao et al., 2020
	Deltamethrin and Atrazine	Zebrafish	Juvenile	6 d	2 μg/L, 3 μg/L	Swimming behavior	Yang et al., 2018
Polychlorinated biphenyls	2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB153)	Zebrafish	Larvae	116 h	0.1 μM	Gene expression; Swimming behavior	Aluru et al., 2020
	PCB mixture	Zebrafish	Adult	250 d	515 ng/g	Swimming behavior	Pean et al., 2013
Neuroactive drugs	Fluoxetine, Sertraline, Venlafaxine	Mosquitofish	Adult	7 d	1 μg/L	Swimming behavior	Melvin, 2017
	Amitriptyline, Fluoxetine, Mianserin	Zebrafish	Larvae	0.5 d, 1 d	0.1 μg/L	Gene expression; Metabolism	Wu et al., 2017
	Diazepam	Zebrafish		3d, 14d	273 ng/L		

(*continued on next page*)

Table 1 (*continued*)

Category	Compound	Fish species	Life stage	Duration of exposure	LOEC	Effect, endpoint	Reference
			Larvae, adult			Gene expression; Swimming behavior	Oggier et al., 2010
Other environmental substances	Cyanopeptolin (CP1020)	Zebrafish	Larvae	1 d	100 μg/L	Gene expression	Faltermann et al., 2014
	Microcystin-LR (MC-LR)	Medaka	Adult	28 d	5 μg/L	Gene expression	Qiao et al., 2016
	Dibutyl phthalate	Goldfish	Adult	6 d	2 μg/L	Swimming behavior	Ren et al., 2019
	Diheptyl phthalate	Zebrafish	Adult	15 d	10 mg/L, 50 mg/L	Swimming behavior; Metabolism	Poopal et al., 2020
	Diisodecyl phthalate	Zebrafish	Adult	15 d	6 mg/L, 30 mg/L	Swimming behavior; Metabolism	Poopal et al., 2020
	Bisphenol A	Killifish	Larvae, adult	60 h	600 μg/L	Gene expression	Rhee et al., 2014
	Bisphenol A	Zebrafish	Adult	2 d	0.1 μM	Social behavior	Weber et al., 2015
	Bisphenol A	Goldfish	Adult	2 d	100 μg/L	Gene expression	Choi et al., 2017

For instance, by use of the transgenic zebrafish, nr1d1:VNP, together with the time-lapse imaging and 3D reconstruction, the sequential initiation of *nr1d1* expression starting at photoreceptors in the pineal gland, then spreading to the cells in other brain regions of zebrafish larvae was firstly observed at the single-cell level during early light exposure (Wang et al., 2020a). In another case, a new fish chamber (behavior sensors) coupled with an online monitoring system (OMS), which enabled the efficiency assessment of real-time behavior responses of zebrafish to different stressors, was employed, and thus, provided a new platform in environmental chemical assessment (Hu et al., 2020; Zhao et al., 2020).

In particular, the evolution of genetic technologies such as CRISPR-Cas9, provides a unprecedented opportunity to explore the environment-clock interactions by generation of mutant animals with aberrant clocks, such as the interaction study between light stimulation and functions of *per* and *timeless* genes (Delventhal et al., 2019). Meanwhile, animals with non-traditional circadian patterns in order to adapt to environments during evolution, such as fish in underground caves and deep-sea environments, also provides new ideas and directions. By comparing these fish with those fish exposed to daily light changes via molecular genetic approaches, our understanding about the environment-clock interaction could be further deepened (Foulkes et al., 2016). For instance, the cavefish, *P. andruzzii*, had an infradian oscillating period, which was regulated by food but not by light. Functional analysis in comparison to zebrafish further pinpointed two extra-retinal photoreceptors, *Opn4m2* and *TMT-opsin*, that were essential upstream elements of the peripheral clock light input pathway (Cavallari et al., 2011).

Furthermore, lowest observed effect concentrations (LOECs) for various endpoints, such as circadian gene expression, physiological alteration and swimming behavior, were observed at environmentally relevant concentrations. For example, LOECs for steroid hormones occurred at concentrations of several to dozens of ng/L. Such concentrations occur in municipal wastewaters or even in strongly polluted surface waters. On the other hand, LOECs for metals, pesticides/biocides and neuroactive drugs occurred at several μg/L. Although being very high, such levels were reported in some waterbodies (Melvin, 2017; Yang et al., 2018; Zhang et al., 2019), suggesting they may pose a risk for dysregulation of the circadian rhythm system of aquatic organisms at some severely contaminated sites. In case of diazepam, low and environmentally relevant concentrations disrupted circadian rhythm regulation and behavior (Oggier et al., 2010). Thus, for some environmental hormones and neuroactive drugs, their environmental concentrations pose a risk for circadian rhythm dysregulation in fish and potentially other aquatic organisms.

Another important implication is the importance of time in experimental studies. Time of the day (and the associated endocrine control by glucocorticoids) is important for controlling circadian rhythms, and thus, is of influence for experimental outcomes. Many genes and functions have a circadian regulation and vary with sampling time. Rhythmicity of endogenous hormones controls other functions. Thus, there is the possibility of false positive or false negative results reported in the literature, as often, time-controlled experimental sampling was lacking, as we highlighted previously (Zhao and Fent, 2016b). Normally, time is not considered as an important parameter in experimental settings and sampling. However, significant artifacts can result, when time is not appropriately considered during sampling. This is mainly due to potential transient transcriptional levels of genes, which display 24 h circadian oscillations (Zhao and Fent, 2016b). Thus, more care should be placed in the future on the timing of and sampling in experiments to obtain better reproducible results.

Our critical review revealed several classes of circadian disrupters, while most environmental substances have not received enough attention and were not analyzed for this effect. Thus, further investigations are needed to fully reveal this underexplored endpoint in ecotoxicology, environmental health and toxicology research. Although many insights have been achieved with zebrafish, their relevance is given for other fish species and for mammals.

Mechanisms of circadian disruption should be further elucidated. Thus far, knowledge about mechanisms of action include interference of environmental chemicals with steroid receptor signaling, AhR signaling and cross-talk with steroid receptors and circadian clock signaling, as well as neuroendocrine regulation. Altered expression of circadian rhythm genes and associated gene products in response to environmental chemical exposure could subsequently affect cellular metabolism leading to alteration of multiple physiological processes (i.e. metabolism, behavior, reproduction). However, links between circadian disruption and physiological outcomes should further be investigated.

Forthcoming studies should focus on and clarify molecular mechanisms underlying circadian disruption, as current studies relate transcriptional alterations to physiological outcomes very rarely. Further attempts should also be made to better understand the correlation between circadian rhythm and physiological processes, as currently, there are little attempts to decipher their causality.

CRediT authorship contribution statement

Xuehan Zheng: Data curation, Visualization. **Kun Zhang:** Data curation, Writing - review & editing, Data curation. **Yanbin Zhao:** Conceptualization, Methodology, Writing, Review & Editing, Supervision, Funding acquisition. **Karl Fent:** Conceptualization, Methodology, Writing, Review & Editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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