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COMMENTARY

Circadian rhythms and environmental disturbances – underexplored interactions

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ABSTRACT

Biological rhythms control the life of virtually all organisms, impacting numerous aspects ranging from subcellular processes to behaviour. Many studies have shown that changes in abiotic environmental conditions can disturb or entrain circadian (~24 h) rhythms. These expected changes are so large that they could impose risks to the long-term viability of populations. Climate change is a major global stressor affecting the fitness of animals, partially because it challenges the adaptive associations between endogenous clocks and temperature – consequently, one can posit that a large-scale natural experiment on the plasticity of rhythm–temperature interactions is underway. Further risks are posed by chemical pollution and the depletion of oxygen levels in aquatic environments. Here, we focused our attention on fish, which are at heightened risk of being affected by human influence and are adapted to diverse environments showing predictable changes in light conditions, oxygen saturation and temperature. The examined literature to date suggests an abundance of mechanisms that can lead to interactions between responses to hypoxia, pollutants or pathogens and regulation of endogenous rhythms, but also reveals gaps in our understanding of the plasticity of endogenous rhythms in fish and in how these interactions may be disturbed by human influence and affect natural populations. Here, we summarize research on the molecular mechanisms behind environment–clock interactions as they relate to oxygen variability, temperature and responses to pollutants, and propose ways to address these interactions more conclusively in future studies.

KEY WORDS: Photoperiod, Climate change, Xenobiotic, PAS protein, Stress, Clock gene

Introduction: why experimental work on environmental effects in fish needs to consider rhythmicity

The light–dark cycle governs many functions of organisms. For example, because animals may be preyed upon during the daytime, some have evolved nocturnal behaviour with associated physiological traits (DeCoursey, 2014; Metcalfe et al., 1999). During the evolutionary history of species at high latitudes, light rhythms have also served as predictable signals of seasonal patterns in environmental temperature – for example, shortening day length in autumn signals that temperatures are about to drop, and the reverse occurs in the spring (Hut and Beersma, 2011). However, climate change affects the photoperiod–temperature relationship and has potential negative consequences for the fitness of organisms (Stevenson et al., 2015). In addition, oxygen deficiency and many chemicals can disturb rhythms that have been adaptive for organisms. This is of significant concern as human actions cause increased chemical and nutrient loads. It is thus evident that timing mechanisms in organisms need to evolve or be plastic in order to continue serving their purpose of improving fitness (Bradshaw and Holzapfel, 2010). However, although human-induced disturbances in the environment may have long-term effects on populations of wild animals through changes in rhythmic regulation, few studies have investigated this. Our aim with this Commentary is to summarize recent literature on the mechanisms of cross-talk between circadian rhythms (see Glossary) and responses to variability in oxygen level and temperature, and to xenobiotics, and to point out several of the knowledge gaps still remaining.

Day–night rhythms in the environment

The 24 h rhythm of sunlight and darkness has been a predictable feature throughout the evolutionary history of life on Earth, and virtually all life forms have adapted to this rhythm (Beale et al., 2016). However, the length of the light period varies markedly at high latitudes, with long day length in the summer and short days in the winter. In polar areas, there is constant darkness in winter and constant light in summer. Changes in photoperiod predict environmental conditions, with decreasing temperatures corresponding to the shortening of day length, and increasing temperatures and day length also coinciding. Thus, responding to changes in environmental light is an important feature of the generation of rhythms in fish. There are two main mechanisms responsible for light sensing in fish – one visual and the other non-visual (see Box 1).

In shallow aquatic environments, a major 24 h rhythm exists not only for light and temperature but also for oxygen availability. Oxygen-producing photosynthesis during the day increases, and respiration by all organisms decreases (especially at night), the oxygen tension (Dejours, 1975). Therefore, the amplitude of the rhythm increases with eutrophication (see Glossary). Light and other predictable daily rhythms entrain circadian clocks, which in turn regulate numerous molecular pathways. In the next section, we outline the cellular mechanisms of regulation by circadian clocks.

An outline of circadian clocks in fish

An endogenous circadian clock exists in organisms ranging from prokaryotes to humans, and among vertebrates the mechanism has been described most comprehensively in mammals (Mohawk et al., 2012; Rutter et al., 2002). This clock serves to synchronize functions, such as behaviour and metabolism, with environmental conditions, thus increasing fitness (Yerushalmi and Green, 2009). The principles for the generation of circadian rhythm in vertebrates, based largely on the mammalian literature, are given in Fig. 1 (for further reviews, see Beale et al. 2016; Buhr and Takahashi, 2013; Lowrey and Takahashi, 2004; Riede et al., 2017; Takahashi, 2017).

The basic circadian rhythm is initially generated by rhythmic positive and negative transcriptional feedback loops. The positive

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Glossary

Circadian
Approximately 24 h ('about a day' in Latin).

Entrainment
Adjustment of circadian rhythms to rhythmic endogenous (internal, such as metabolic status) or exogenous (external, such as ambient temperature) signals.

Environmental response
The physiological or molecular response mounted by an organism facing changes in temperature, oxygen availability, light or other abiotic conditions in its surrounding environment.

Eutrophication
An increase in primary production caused by nutrient input and/or increased temperature in aquatic environments, leading to both an increase in the amplitude of variation in the dissolved oxygen level because of increased photosynthesis during the light period and increased respiration at night, and an overall reduction in the level of dissolved oxygen due to the decomposition of organic matter.

Hypoxia
Decreased availability of oxygen in air/water. Especially in water-breathing animals, the oxygen saturation considered hypoxic is very species specific. In an active salmonid, an oxygen level below 50% of air saturation can be considered hypoxia, whereas in a tolerant cyprinid, hypoxia responses start to appear only when air saturation drops below 10%.

microRNA
A short (~20–30 nucleotide) non-coding RNA molecule that usually regulates mRNA abundance but can also affect the efficiency of translation of mRNA into protein in cells.

PAS protein
A protein having in its sequence one or several so-called PER-ARNT-SIM (PAS) repeats (i.e. PAS domains), which are approximately 70 amino acids long.

Redox cycle
Oscillation in the cellular reduction–oxidation environment, caused by the accumulation of reactive oxygen and nitrogen species (ROS and RNS) and by their removal by antioxidants.

Temperature compensation
A significant reduction in the variability of period length of circadian rhythms over a range of temperatures. Without temperature compensation, increasing temperature would shorten period length and the opposite would occur with decreasing temperature.

Xenobiotic
A chemical compound introduced into the environment by humans, or a compound found within an organism but originating from outside it.

Zeitgeber
A signal that can set (entrain) the phase of circadian clocks in organisms.

Box 1. How is light information perceived by fish?

Light is the best-known environmental regulator of circadian rhythms. In contrast to mammals, in which light perception through the eyes is necessary for circadian clock entrainment, circadian clocks of isolated peripheral tissues from fish can be directly entrained by light (Whitmore et al., 2000). This property, also observed in isolated cell lines, is a valuable feature for understanding the mechanisms behind light sensing (Foulkes et al., 2016). Two main mechanisms are responsible for light sensing in fish: visual photoreception through the retinohypothalamic tract from the retina to the brain and non-visual photoreception in deep brain and peripheral tissues (Fernandes et al., 2013). The extra-retinal photoreceptors can receive information on light angle, irradiance or polarization. They usually belong to a class of G-protein-coupled receptors called opsins, and have thus far been described in lizards, amphibians and birds in addition to fish (Peirson et al., 2009). Non-visual photoreception could be important for interpreting time-of-day, and it is probably an evolutionarily ancient mechanism (Peirson et al., 2009).

loop that activates gene expression has as its gene products the transcription factors 'circadian locomotor cycles kaput' (CLOCK) and 'aryl hydrocarbon receptor nuclear translocator-like protein 1' (ARNTL, aka BMAL/MOP3; homologue of CYCLE in the fruit fly *Drosophila*; McIntosh et al., 2010) (Fig. 1). These transcription factors bind to E-box elements in the promoter regions of thousands of genes in a ~24 h rhythm (Koike et al., 2012; Yoshitane et al., 2014). Although multiple genes are expressed with circadian rhythm, the DNA binding of CLOCK and ARNTL to the E-box elements of the negative loop genes encoding the proteins period (PER) and cryptochrome (CRY) and inducing their transcription is decisive for the generation of the circadian rhythm. CLOCK also has chromatin-modifying properties that are enhanced by ARNTL (Doi et al., 2006). PER and CRY decrease the activity of CLOCK and ARNTL, thereby repressing their own expression (Mohawk et al., 2012), which constitutes the negative feedback loop. The mechanism by which PER and CRY inhibit the activity of the CLOCK–ARNTL dimer involves many proteins from the Mi-2–nucleosome remodelling and deacetylase transcriptional co-repressor complex; a detailed model of proteins involved in the feedback loops in mammals has been presented by Takahashi (2017).

Although the basic generation of circadian rhythms involves the rhythmic transcription of genes in the positive- and negative-feedback loops, fine-tuning of the rhythms occurs by many post-transcriptional and epigenetic mechanisms (Alvarez-Saavedra et al., 2011; Beckwith and Yanovsky, 2014; Feng and Lazar, 2012; Lee et al., 2001; Ripperger and Merrow, 2011), including the function of both microRNAs (see Glossary) and long non-coding RNAs (Coon et al., 2012; Liu and Wang, 2012; Pegoraro and Tauber, 2008; Shende et al., 2014; Wu et al., 2018). Because one function of circadian rhythms is to integrate metabolism with environmental conditions, the rhythms are closely associated with metabolism (Bailey et al., 2014; Feng and Lazar, 2012; Rey and Reddy, 2013; Rutter et al., 2002) and nutrition (Johnston, 2014). In particular, cytosolic redox cycles (see Glossary) (Bailey et al., 2014; Rutter et al., 2001), which are affected by metabolism, are important components of circadian clocks. Note that circadian rhythms can persist even without rhythmic transcription in mammalian red blood cells and primitive eukaryotic cells (O'Neill and Reddy, 2011; O'Neill et al., 2011) – and, in these cases, the generation of rhythm depends on a redox cycle. However, the importance of similarly generated rhythms in multicellular systems with nuclei remains poorly understood.

The dependence of clock function on metabolism is one of the factors that causes interactions between environmental changes and circadian rhythms. Another significant factor is that the major regulatory transcription factors behind the circadian clock, CLOCK and ARNTL, belong to the PER-ARNT-SIM (PAS, see Glossary) group of transcription factors, which regulate many transcriptional responses to changes in the environment (Gu et al., 2000). Cross-dimerization can occur between clock proteins and other transcription factors with PAS domains (Hogenesch et al., 1998). For instance, a PAS-domain transcription factor, hypoxia-inducible factor 1 (HIF-1), can bind to the E-box elements in the promoter region of *per1* (where CLOCK normally binds) in zebrafish, thus modifying *per* transcription (Egg et al., 2013); although this has so far only been studied in one fish species, it could be a general phenomenon. Another PAS-domain transcription factor, aryl hydrocarbon receptor, is a major component of detoxification pathways in fish (Hahn, 2002) and has been shown to interact with circadian clock proteins in mammalian tissues (e.g. Claudel et al.,

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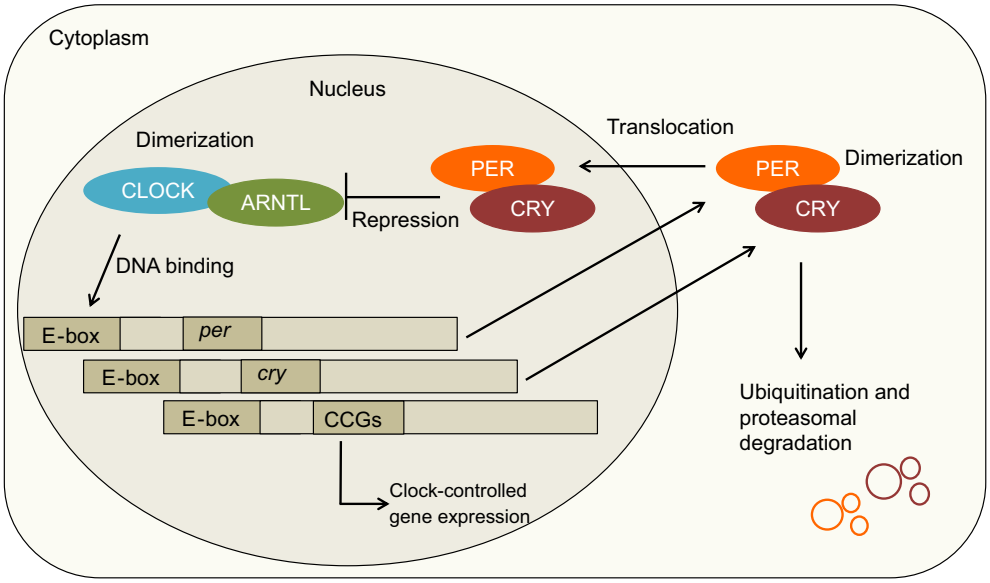

Fig. 1. The regulatory feedback loops of circadian rhythms. In fish, multiple paralogues of each circadian clock protein may exist owing to whole-genome duplications. Constitutively expressed CLOCK dimerizes with ARNTL (aka BMAL) in the nucleus and binds to E-box elements in the promoter regions of *per*, *cry* and other clock-controlled genes. PER and CRY proteins dimerize in the cytoplasm, and the dimer translocates to the nucleus. The accumulation of PER–CRY dimers is partly controlled by ubiquitination and degradation of the proteins. In the nucleus, PER and CRY inhibit the activity of the CLOCK–ARNTL dimer, eventually allowing the transcriptional cycle to restart. ARNTL expression is also affected by another transcriptional loop, including genes encoding the proteins RAR-related orphan receptor A (RORA) and nuclear receptor subfamily 1 group D member 1 (NR1D1) (not shown). Modified from McIntosh et al. (2010).

2007; Tischkau et al., 2011) and with HIF-1 in mammalian and fish cells (e.g. Fleming et al., 2009; Nie et al., 2001).

Although the basic principles of circadian clock function are likely to be the same in mammals and fish, as the main players are largely conserved in eukaryotes (Dunlap, 1998), the clocks in fish might be more versatile than those in mammals. This is because: (1) fish have minimally had one genome-wide gene duplication more than mammals; fish seem to have more clock genes than mammals and thus subfunctionalization of gene duplicates (paralogues) could have occurred (Toloza-Villalobos et al., 2015; Wang, 2008a,b, 2009; Vatine et al., 2011); (2) as fish are ectotherms and adapted to a huge variety of temperature rhythms, their clocks must acclimatize to varying temperatures (Lahiri et al., 2005); and (3) in addition to the retinal photoreceptors, which generally mediate light information in vertebrates, in fish the pineal gland and peripheral tissues are also sensitive to light (Box 1) (Foulkes et al., 2016; Vatine et al., 2011).

Endocrine control of circadian rhythms influences experimental results

Many functions have circadian rhythms – 10–20% of the expressed genome can have circadian regulation (Reddy et al., 2006). Consequently, many physiological parameters of animals vary depending on the sampling time. The endocrine system is responsible for mediating much of this variation (Challet, 2015), which is also reflected in responses to environmental disturbances (Zhao and Fent, 2016). As the rhythmicity of endocrine function in fish has recently been reviewed (Cowan et al., 2017), we will not cover the topic in detail here. Thus, although cortisol, thyroid hormones, reproductive hormones and hormones of the gastrointestinal tract show rhythmicity (Cowan et al., 2017), they are not discussed further. Endocrine rhythms can vary markedly between individuals, as demonstrated by the time-dependent variation of blood growth hormone level in specimens of the grass carp *Ctenopharyngodon idellus* (Zhang et al., 1994). Grass carps were catheterized via the dorsal aorta, enabling serial blood sampling, and individual peak excretion time of the hormone assessed. By this means, it was shown that individual variability, often taken to be only undesirable ‘noise’, can be a significant contributor to the ability of fish to tolerate environmental changes. However, even when serial blood samples were obtained, no rhythmicity was observed in the growth hormone concentration in rainbow trout (Gomez et al., 1996). This finding suggests that there are species-specific differences in the pattern of growth hormone excretion in fish. Notably, these growth hormone studies did not focus on studying whether season could affect rhythmicity. This is significant as seasonal (reproductive phase-, light- and temperature-dependent) effects have been observed in the secretion of, or responses to, many hormones (Cowan et al., 2017).

Melatonin is known as the ‘time-keeper hormone’ in vertebrates as it regulates rhythms such as the sleep–wake cycle. It is synthesized from serotonin by the enzyme arylalkylamine *N*-acetyltransferase (AANAT) in the pineal gland (Falcón et al., 2010, 2011). In fish, AANAT2 in particular is responsible for the oscillating pattern of melatonin synthesis that peaks in the dark (Falcón et al., 2011). Indeed, light-rhythm-dependent changes in melatonin level have been found in the plasma, gut or pineal gland of many teleost species *in vivo* and *in vitro* (Choi et al., 2016; Huang et al., 2010; Kezuka et al., 1988; Pal et al., 2016; Strand et al., 2008). The circadian clock establishes rhythms of melatonin production, but melatonin rhythms are highly species dependent – species with different life histories and activity rhythms can differ in the regulation of melatonin synthesis and in its effects on behaviour (Iigo et al., 2007; López-Olmeda et al., 2006). Melatonin can participate in integrating circadian clocks and metabolism (Barnea et al., 2012) as it can function as an antioxidant and as redox balance affects circadian clock function and its coupling to metabolism (Bailey et al., 2014). In fish, nutritional variations, circadian

rhythms and changes in melatonin levels have been implicated in variations in the levels of oxygen free radicals (Choi et al., 2016; Pal et al., 2016). The finding that melatonin (and many hormones of the gastrointestinal tract) affects redox balance indicates that there can be pronounced interaction between endocrine functions, their rhythmicity and pollutants that cause oxidative stress.

Climate change and biological rhythms

Circadian rhythms

Studies on circadian/daily rhythms and temperature change in fish have predominantly looked either at variations of activity when both day length and temperature change (Reebs, 2002) or at the molecular effects of temperature cycles on circadian rhythm (Lahiri et al., 2005). However, the effects of a change of temperature on rhythmicity at fixed photoperiods have been little studied. Furthermore, studies on the temperature–clock relationship in fish have concentrated on the (sub)tropical zebrafish, which has experienced relatively constant day length during evolution. Consequently, little is known regarding whether temperature affects circadian responses differently in species, other than zebrafish, that have evolved in environments with large seasonal variations of day length.

A decrease in temperature can decrease or abolish rhythmicity of organisms (Murayama et al., 2017; Rensing and Ruoff, 2002; Vallone et al., 2007). Accordingly, it has recently been shown that the daily variation of transcription in a polar salmonid, the Arctic char (*Salvelinus alpinus*), is much reduced after a 1 month acclimation to 8°C in comparison with acclimation to 15°C (Fig. 2) (Prokkola et al., 2018).

The finding that rhythmicity decreases with decreasing temperature when the day length decreases agrees with changes observed in the activity of Arctic char in polar areas (Hawley et al., 2017) – the activity rhythm disappeared at cold temperatures during the polar night. However, it also disappeared in the polar day, despite the increasing water temperature, indicating that the light–temperature relationship is complex. Based on these results, changes in the light–temperature relationship might have pronounced, but poorly predictable, effects on the rhythmicity of transcription and functions that are dependent on the integration of light cues and rhythmic gene expression.

The relationship between circadian rhythms and temperature is made even more complex by the fact that rhythms are often ‘temperature compensated’ (Pittendrigh and Caldarola, 1973). Because of the general temperature compensation (see Glossary), for example, the fish heart functions appropriately both in winter- and summer-acclimated fish (Badr et al., 2016). It is currently not known how changes in the day length–temperature relationship are reflected in temperature compensation.

Finally, the effects of temperature on rhythmicity have often been addressed at the level of behaviour, or other integrative functions that involve many proteins. However, changes in transcription and in protein production, and the rhythms of these processes, often show poor correlation (Rey and Reddy, 2013). Further, even the effects of constant temperature on the relationship between transcription and translation are not clear (Lewis et al., 2016). Therefore, relating temperature effects on single genes to integrative rhythmic phenomena is difficult, but should be pursued further. There is also marked individual variability in the rhythmic responses, as fish from the same batch can be nocturnal, diurnal or aphasic (Reebs, 2002). The reasons for this variability are poorly known (i.e. whether they are caused by genetic variations in a population or by phenotypic plasticity of a genotype), as are the effects of temperature on it.

Circannual rhythms

Climate change affects the relationship between day length and temperature by causing temperatures to increase at a given latitude and by increasing the frequency of extreme weather events (IPCC, 2013). Based solely on the effects of temperature on the physiology of ectotherms, an increase of temperature should increase the fitness of animals (Bradshaw and Holzapfel, 2010), if there are no resource limitations. At a given latitude, photoperiod remains unchanged even when the temperature is affected. Consequently, assuming that temperature responses can be regulated by seasonal rhythms, endogenous clocks must be able to adjust to the changes in the light–temperature relationship, or otherwise the responses take place in inappropriate light/temperature conditions and can cause fitness costs through, for example, breeding at an unsuitable time of season with respect to food abundance (Bradshaw and Holzapfel, 2010). This also applies to fish; although they live in water, where light penetration is poor, most species live in the photic zone. A good example of a seasonal light–temperature relationship is the regulation of growth hormone and antifreeze protein production in the flounder (e.g. Fletcher et al., 2001). Antifreeze proteins allow many ectothermic animals to survive at sub-zero temperatures. In flounder, the transcription of the gene encoding anti-freeze protein is mainly regulated by day length. However, as the produced mRNA is only translated to the protein at low temperatures, alterations in the day length–temperature relationship will affect the production of antifreeze protein.

From the research conducted on temperature responses and circadian rhythms in fishes to date, the conclusion is that well-understood features are far outnumbered by more poorly understood relationships. In particular, the knowledge gaps relating to the mechanisms and the generality of temperature compensation in species adapted to seasonally variable environments should be addressed urgently.

Variability in oxygen level requires adaptations in biological clock function

The amplitude of circadian cycles is generally reduced by hypoxia (see Glossary) (Mortola, 2007). Hypoxia can also reverse circadian rhythms in the spontaneous activity of fish (Svendsen et al., 2014). While many interactions between hypoxia and circadian rhythms remain to be clarified, one mechanism is quite clear. Both hypoxia and circadian responses depend critically on transcriptional regulation by the respective PAS-domain transcription factors (McIntosh et al., 2010). The transcriptional regulators interact; recent studies on mouse have shown that manipulations of HIF1α affect circadian transcriptional rhythms, and manipulations of ARNTL affect anaerobic glycolysis (Peek et al., 2017). Likewise, oxygen rhythms reset clocks in cultured mouse cells in a HIF1α-dependent manner (Adamovich et al., 2017). In zebrafish, the hypoxia response is decreased if the rhythms of fish are disturbed in comparison with fish with intact rhythms (Egg et al., 2014). Because of the competitive binding of HIF1α to the same sequence in the promoter region of *Per* genes to that bound by CLOCK, the circadian rhythm of *Per* transcription is dampened in hypoxic conditions (Egg et al., 2013; Pelster and Egg, 2015). Probable HIF–CLOCK–PER interactions have been demonstrated in mouse (Chilov et al., 2001), and several forms of cancer appear to involve aberrant interactions between hypoxia and rhythmic gene expression (Mazzoccoli et al., 2014; Yu et al., 2015). Consequently, it is evident that there is a close relationship between hypoxia responses and the circadian clock, regardless of the species.

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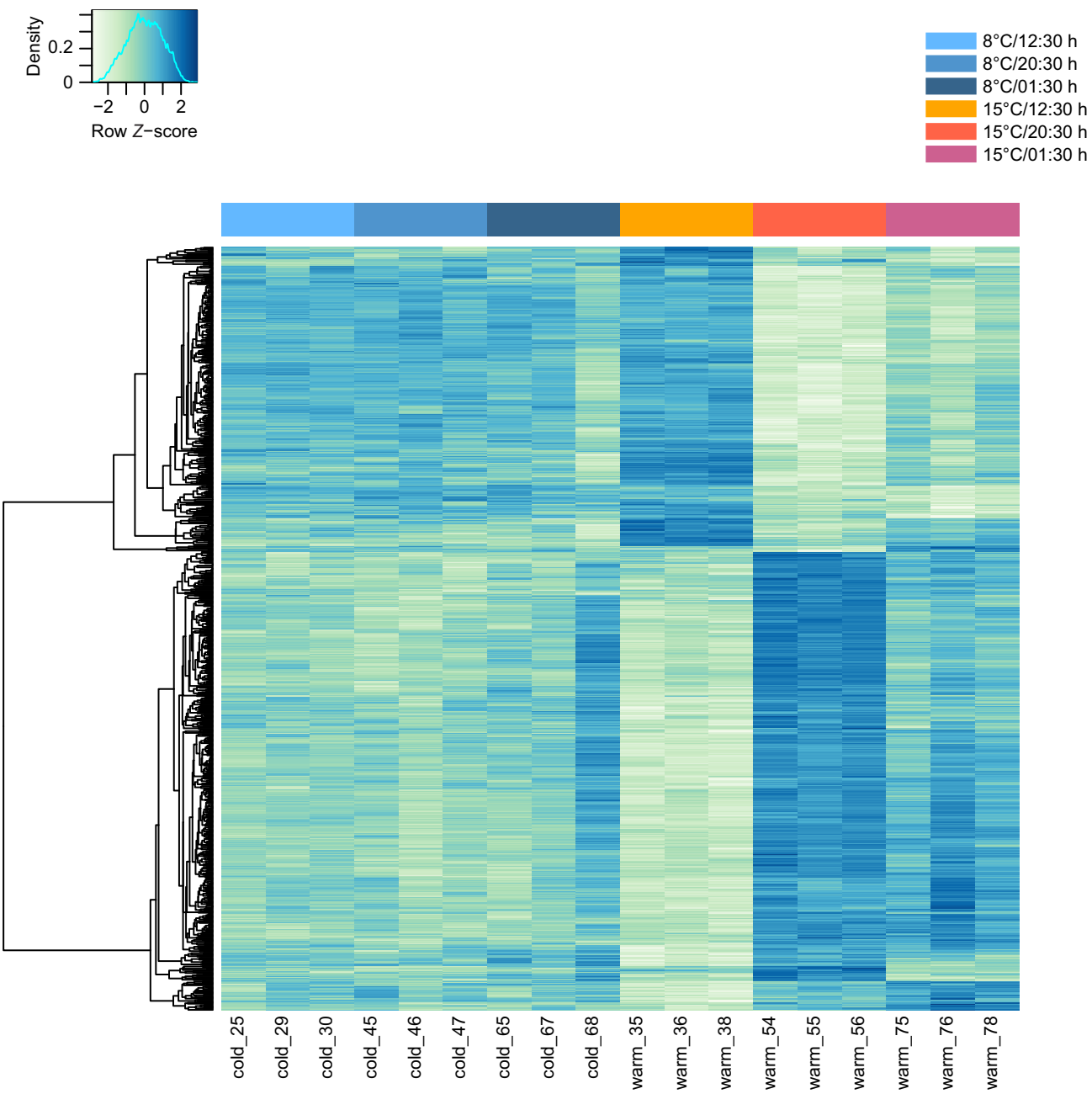

Fig. 2. Heatmap showing standardized mRNA levels of genes with significant temporal variation (false discovery rate, FDR <0.01) between three time points in the liver of the Arctic char *Salvelinus alpinus* acclimated at 15°C for 1 month, measured using RNA sequencing. At 15°C, 747 rows (genes) showed temporal variation. In contrast, in fish held at 8°C for a month, no genes were differentially expressed between time-points at this FDR. Data are from Prokkola et al. (2018).

Toxic chemicals and their effects upon circadian rhythms

The interactions between chemical toxicity and circadian rhythm are generally caused either by the enzymes of detoxification pathways showing rhythmic activity or xenobiotics (see Glossary) disturbing the generation of rhythms (Claudel et al., 2007; Lim et al., 2006). A schematic diagram of the disturbances is given in Fig. 3.

The most obvious example of xenobiotics disturbing circadian rhythms involves the most-studied biotransformation pathway in fish – the aryl hydrocarbon receptor-dependent detoxification pathway (Schlenk et al., 2008), in which the transcription factor AhR is the major initiator. AhR belongs to the same family of PAS proteins as CLOCK and ARNTL (BMAL) (Fig. 4) (McIntosh et al., 2010) and influences the production of an enzyme, cytochrome P450 1A (CYP1A), which oxidizes xenobiotics in biotransformation.

CYP1A activity shows daily variation in the liver of the three-spine stickleback under control conditions (Fig. 5), either as a result of direct interaction between AhR and circadian clock pathways or owing to other metabolic interactions (Prokkola et al., 2015).

Daily variation and changes in detoxification efficiency could also be driven by reactive oxygen species (ROS), which can change the redox balance of cells and be influenced by chemicals (Bailey et al., 2014). Based on studies in mammals, it can be hypothesized that nutritional status and toxicants obtained in food can be linked to disturbances in the circadian clock function through redox cycles

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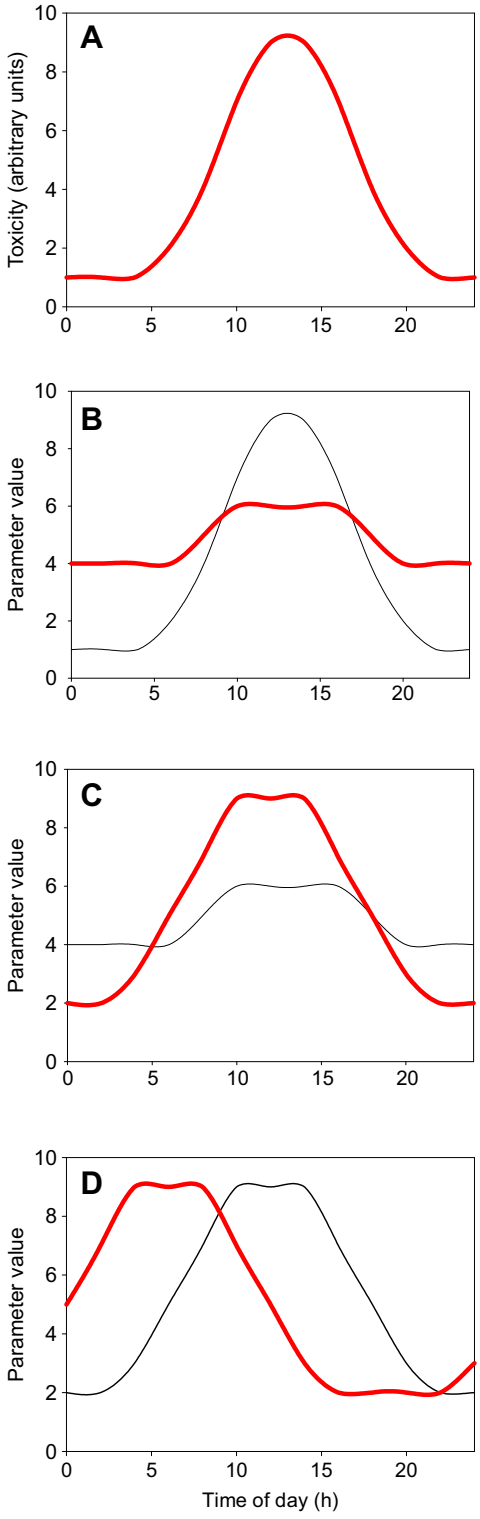

Fig. 3. Schematic diagram showing various ways in which chemicals can interact with circadian rhythms. (A) Toxicity conforms to a circadian rhythm. (B) The amplitude of the rhythm of a parameter is reduced. (C) The amplitude of the rhythm of a parameter is increased. (D) The timing of the circadian rhythm of a parameter is shifted. Note that combinations of A–D may occur. Xenobiotic exposures are represented by red lines.

(Claudel et al., 2007; Rutter et al., 2002). Moreover, there is evidence that peripheral clocks (i.e. circadian clocks in tissues outside the central pacemaker), for which nutritional/metabolic

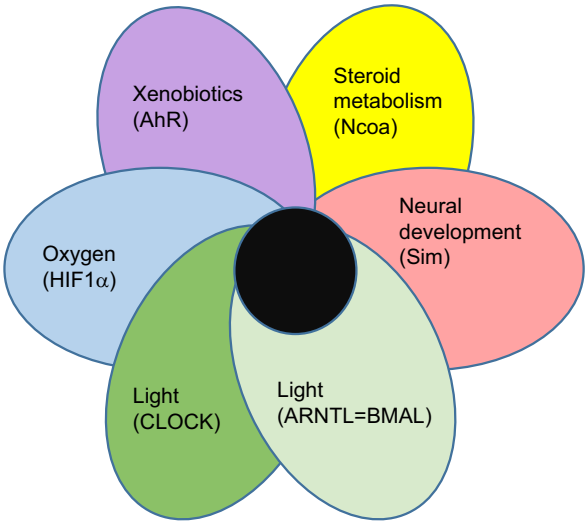

Fig. 4. Examples of the central PAS-domain proteins regulating environmental responses transcriptionally in vertebrates. The PAS domain is represented by the black circle, indicating that all the members of the family have the PAS domain in their structure. The main factor to which the protein is responsive is indicated in each case. In addition to the depicted proteins, there are also several other PAS-family proteins with various functions in animals.

status is a very important zeitgeber (see Glossary), affect xenobiotic metabolism (DeBruyne et al., 2014). While most of the studies on daily rhythms in chemical effects and toxicity are drug studies in humans and other mammals (Kitoh et al., 2005; Ohmori and Fujimura, 2005), it is probable that circadian variations in the toxicities of pollutants in aquatic ecosystems also occur.

Several authors have demonstrated daily variation in the effects of xenobiotics on fish. Endocrine-disrupting chemicals perturb the oscillation patterns of the transcription of putatively rhythm-generating genes in mangrove killifish (Rhee et al., 2014). Environmental progestins (synthetic progestogen drugs) alter the

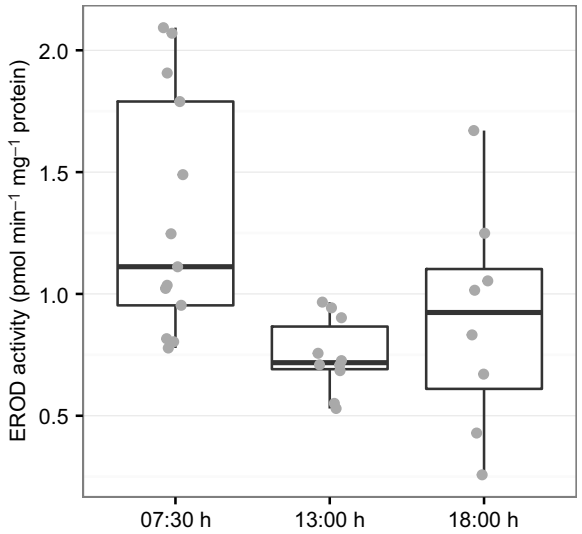

Fig. 5. The activity of CYP1A as measured by ethoxyresorufin O-deethylase (EROD) assay in the liver of three-spined stickleback under normoxic conditions. Samples were collected at three time points; light period from 07:00 h to 19:00 h. It can be concluded that the EROD activity at 07:30 h is significantly higher than that at 13:00 h (P=0.006, MCMCglmm; Prokkola et al., 2015). Data from Prokkola et al. (2015).

transcription of rhythm-generating genes in zebrafish (Zhao et al., 2015) and wastewater treatment plant effluent can reduce circadian oscillation in the activity of male mosquitofish (Melvin et al., 2016). In addition, the anti-inflammatory drug diclofenac disturbs the temporal patterns of transcription of rhythm-generating genes and, for example, lactate dehydrogenase activity, in three-spined stickleback (Lubiana et al., 2016; Prokkola et al., 2015). Hence, ecotoxicological research can provide valuable insight on the importance of circadian rhythms across tissues in fish. Importantly, the same applies to studying diseases and the function of immune systems.

Immunoresponses can be regulated by the circadian clock

Both humoral and cellular immune systems show circadian rhythms (Scheiermann et al., 2013). While these rhythms have been especially well studied in humans, they are also found in fish (Esteban et al., 2006; Lazado et al., 2016; Preussner and Heyd, 2016). There appears to be a close interaction between circadian rhythms in hormonal function and immunological effects (Scheiermann et al., 2013). A good example is that circadian rhythms of immune function in fish have been explained by changes in circulating melatonin concentration – that is, with pineal gland function (Esteban et al., 2006). Moreover, endocrine-disrupting agents could be behind immunological disturbances, as shown for environmental corticosteroid analogues in zebrafish (Zhao et al., 2016).

Because of the interactions between rhythms and immune function in fish and other organisms, the intensity of infections and disease symptoms varies partly as a result of endogenous rhythms in addition to other sources of variation originating from the host, the pathogen and the environment (including the effects of xenobiotics). The highest investment in immune defence should occur during the time when exposure to pathogens is the greatest. This is expected to coincide with the season of highest activity or the time of highest food intake and social contact, which depends mainly on social, feeding and breeding behaviour. Therefore, knowledge on the ecology and habitat of studied species helps towards predicting how different environmental changes and contaminants could affect the immunological balance, and thereby the fitness, of an organism.

Concluding remarks: addressing temporal variation should be a must in future studies of environmental responses

Circadian rhythms and their disturbances are an integral part of environmental responses (see Glossary). Despite this, the majority of environmental studies have not taken the rhythmic circadian and seasonal variation into account. Often, only a single time point has been studied in each experiment, although it is clear that a single time point cannot describe any circadian rhythm of the response. This practice can lead to a situation where variation that can be dramatic and important for the investigated physiological or behavioural response is ignored. Although multiple sampling time points across several daily cycles are therefore recommended, even three time points can indicate whether important variation is ignored if the study setup is limited to a single time point, as shown in Healy and Schulte (2012), Lewis et al. (2016), Lubiana et al. (2016) and Prokkola et al. (2015, 2018).

As a minimum, it is imperative that a control group is always sampled at the same time point as experimental groups. (A control group is naturally always used in experimental studies, but the importance of its time of sampling has not been emphasized.) Furthermore, comparing results of studies with different light–dark rhythms and temperatures should be done while acknowledging that both can affect the rhythmicity of responses. Notably, seasonal comparisons can also be confounded by daily variation if a single time point is investigated between seasons without accounting for daily variation.

To control for the effects of feeding in measured variables, randomized feeding regimes are useful, as feeding affects, for example, the rhythmic expression of microRNAs, which can regulate many circadian patterns (Wu et al., 2018). However, the entrainment effect (see Glossary) of rhythmic feeding may be limited to clocks in peripheral tissues, as shown in mammals (reviewed in Schibler and Sassone-Corsi, 2002; Potter et al., 2016). Furthermore, as nutritional status affects peripheral rhythms, the standard use of, for example, fish starved for 24 h might give results different from those that would be observed with fed fish.

For species adapted to shallow aquatic environments, fluctuating temperatures and oxygen levels are more a rule than an exception in the natural habitat. Additionally, manipulation of entrainment cues (e.g. photoperiod or temperature rhythm) can reveal the negative effects/costs of not being able to entrain responses to the environment. Thus, changing the zeitgebers to disturb endogenous clocks will affect the processes that are coupled to circadian rhythms. For example, photoperiods are often manipulated in aquaculture to maintain individuals at the desired life stage and growth rate (Davie et al., 2007; Kråkenes et al., 1991), which demonstrates that, by manipulating this single zeitgeber, the physiological state of the whole organism can be drastically altered.

Thus, over the decades to come, we will begin to see how the increasing unpredictability in seasonal weather patterns affects wildlife. Considering the close relationships of rhythms, metabolism and environmental responses in fish, it would be no surprise if subtle changes in multiple abiotic conditions had cascading effects on life-history traits, with notable effects on populations. Finally, because circadian rhythms are expected to have high adaptive value (Yerushalmi and Green, 2009), future studies must continue to clarify how disturbances in clock function affect the fitness of organisms.

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Competing interests

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